THE
LARYNGOSCOPE.

VOL. LXX APRIL, 1960 No. 4

Workshop on the Inner Ear.

THE HISTOCHEMISTRY OF THE ENZYMES OF OXYGEN METABOLISM IN THE INNER EAR.*†

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One of the most interesting problems in the biology of the cochlea is the study of chemical sources of energy. From the transformation of sound in the cochlea, it is known that the energy which is transferred to the nervous system is greater than that received from the cochlea. The only possibility for this energy increase is a chemical metabolic process. Almost all metabolic reactions receive their energy from the oxygen metabolism (respiration of the cell). This metabolism depends again upon the activity of its enzyme systems.

Using histochemical techniques we can investigate the respiratory function of a cell and so demonstrate the sites of energy production; therefore, histochemistry can supply valuable insight into the transformation of energy in the cochlea.

Cell respiration is a chain reaction, during which individual organic substrates loose their hydrogen atom by specific enzymatic processes. The hydrogen is then carried by the coenzymes DPN and TPN, with the assistance of diaphorase, to the cytochromes, or is directly delivered by means of succinodehydrogenase. By reoxydation of the cytochromes and

*Read at the meeting of the Middle Section, American Laryngological, Rhinological and Otological Society, Inc., Chicago, Ill., Jan. 18, 1960.

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Editor's Note: This manuscript received in The Laryngoscope Office and accepted for publication March 10, 1960.

with the assistance of the cytochromoxydase the hydrogen can finally be eliminated as water.

The most important respiratory enzymes, namely the cytochromoxydase, the succinodehydrogenase and the diaphorases can be histochemically demonstrated.

The method for cytochromoxydase is one of the oldest histochemical procedures. More than 40 years ago Graeff[7] showed

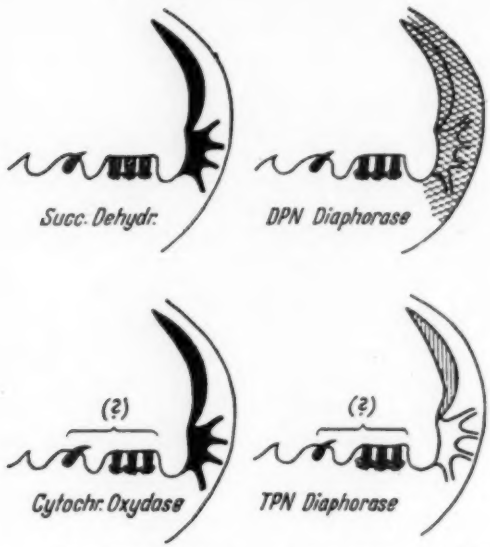

Fig. 1. Distribution of the enzymes of oxygen metabolism.

that a mixture of x-naphthol and dimethylparaphenylendiamin can be oxydized by the oxydase to indophenol-blue. This indophenol-blue appears in histochemical preparations only where considerable amounts of oxydase are localized. By blocking with potassium cyanide we can specifically test for cytochromoxydase.

The histochemical procedure for succinodehydrogenase was worked out by Rutenburg and Seligmann.[12] It is based on the fact that a colorless tetrazolium salt is reduced in the presence

of dehydrating enzymes to the colored formazan. By using succinic acid as a substrate and by elimination of the other hydrogen donors this test can be made specific. The blue-red formazan crystals can also be found in areas where great amounts of succinodehydrogenase are concentrated, for example in the stria vascularis. A specific control can be achieved by pre-treatment of the slides with sodium malonate.

The method for the demonstration of diaphorase uses the same principles. A tetrazolium salt again serves as an indicator. The use of the coenzymes DPN and TPN in the

Fig. 2. Ductus cochlearis, succinodehydrogenase.

medium makes this test specific. According to Farber, Sternberg and Dunlap[3] other substrates have been added to get more pronounced effects.

The respiratory enzymes are very sensitive and, therefore, the histochemical reactions can be carried out only with fresh and unfixed material. Immediately after death of the animal—we have used guinea pigs exclusively—one must separate parts of the ductus cochlearis by microdissection and cut frozen sections.[19]

Fig. 3. Stria vascularis, succinodehydrogenase.

The distribution of the enzymes can be recognized in such a frozen section through the ductus cochlearis. The succinodehydrogenase shows, for example, its strongest concentration in the stria vascularis and in a part of the ligamentum spirale behind the sulcus externus and in the hair cells.

The typical patterns of distribution of the other respiratory enzymes are shown in a diagram. Cytochrome-oxydase and succinodehydrogenase are concentrated in the same place: the stria vascularis, behind the sulcus externus and the hair cells.

The diaphorases show a different pattern of distribution.

A very strong accumulation is to be found in the hair cells also, but in the stria vascularis only the DPN-diaphorase is especially active, and the areas behind the sulcus externus show no strong staining reaction.

All these enzymes are links of the same chain reaction and therefore, it is surprising that they are not concentrated in

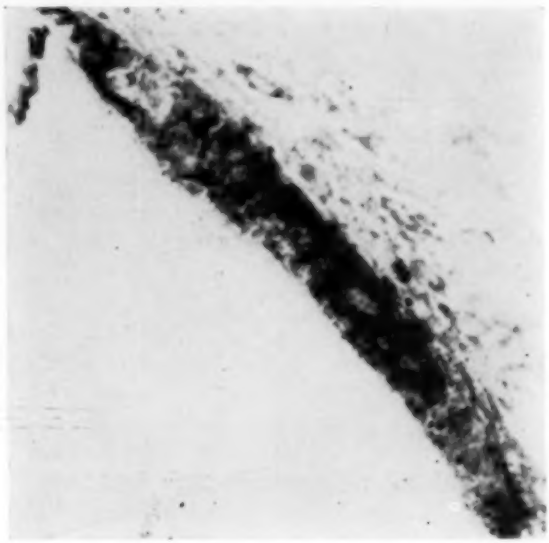

Fig. 4. Stria vascularis, TPN-diaphorase.

the same location. The dehydrogenase and oxydase are always found in the same spot. In other organs, for example the liver[13] and the kidney,[5] it has been demonstrated that the diaphorase shows a different pattern of distribution. An explanation for this phenomenon can not be offered at this time. Comparative histochemical and biochemical investigations have shown that the intensity of respiratory processes always runs parallel with the activity of succinodehydrogenase and cytochromoxydase.

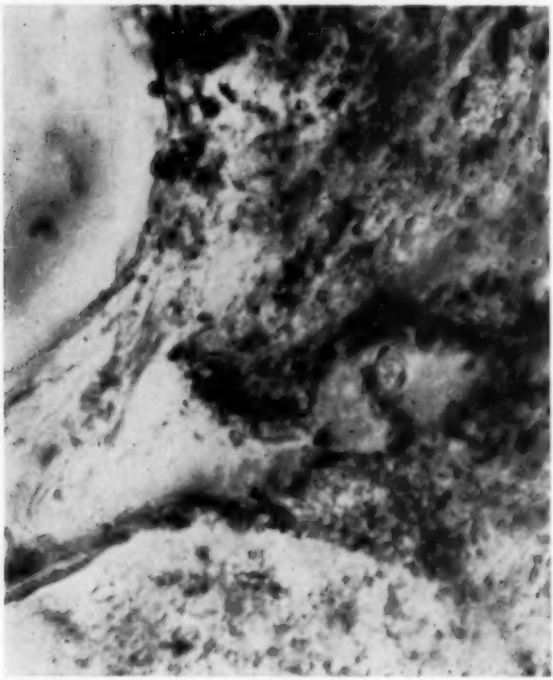

Fig. 5. Sulcus externus with a glandlike canal. Succinodehydrogenase.

In the sensory cells the diaphorase also is distributed differently from the dehydrogenases. In the case of DPN-diaphorase for example, one sees that the whole cytoplasm of the cells is filled with enzyme while the surrounding areas remain free. The succinodehydrogenase on the other hand is very strongly concentrated in the basis of the outer hair cells and also in the areas surrounding these bases.

From electronmicroscopic pictures we know that the basis of the outer hair cells contains many mitochondria.[4] The nerve endings of the cochlear nerve which surround the bases of the outer hair cells are also filled with mitochondria. If we compare such electronmicroscopic pictures with histochemi-

Fig. 6. Corti organ, Succinodehydrogenase.

cal preparations we can recognize that the areas outside the hair-cells represent the nerve endings. One may, therefore, conclude that one of the energy sources for the sound transformation is to be found here because of the strong concentration of respiratory enzymes in these areas.

From observations of other organs we know[17] that an increased functional strain can cause a change of the activity of the respiratory enzymes; similar changes can be readily examined in the inner ear. There we are in a rather unique position for evaluating changes of different parts, some of which react selectively to the applied stimulus, whereas other

areas, which are not affected by treatment, can serve also as controls in the same organ of the same animal.

Actually after stimulation with pure tones with an intensity range of approximately 75 to 85 db for two days we can recognize the first changes in the enzyme profile of the Corti organ.[22] In the responding areas there can be found numerous outer hair cells with decreased dehydrogenase activity,

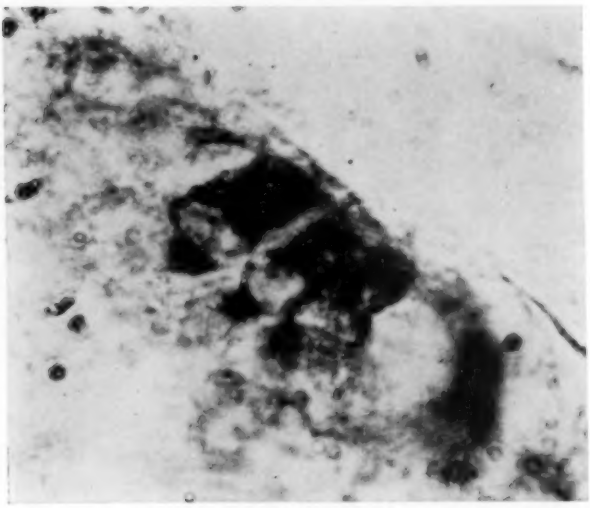

Fig. 7. Outer hair cells, DPN-diaphorase.

especially in the areas of the cell bases and the immediate structures, the nerve endings. With increasing duration or intensity these findings become more pronounced. At first one sees a few destroyed sensory cells in the center of the respective area, the number of which later will increase considerably. Many sensory cells remain unchanged when evaluated by conventional light microscopy. Histochemically, however, a few changes are already noticeable. Sometimes the enzyme reaction fails only in the area of the nerve endings while the hair cells themselves are nicely stained. In other

instances the sensory cells also have lost their enzymatic activity which is always accompanied by the aforementioned changes of the nerve endings. After approximately eight to ten days finally all external hair cells in the exposed area are destroyed, and only the inner hair cells remain unchanged.

If one allows an animal to live four to six weeks after termination of the exposure, the same histochemical changes can be observed as in animals which have been sacrificed immediately after exposure.

These observations indicate the following time sequence in the development of the damage to hair cells. The first histochemical findings after experimental exposure to sound represent a decrease of the respiratory enzyme in the nerve endings. In later stages the entire outer hair cells are also affected, and the complete destruction of these specific cellular elements finally follows.

These changes occur only after the exposure to a continuous tone. If this tone is rhythmically interrupted, so that after an impulse which lasts 250 milliseconds we allow a 250 millisecond interval, the described effect then can be avoided. The interpretation of the findings is not very difficult. The destruction of the outer hair cells following an acoustic trauma under these conditions is not the result of a mechanical injury but rather the result of a complete exhaustion of the metabolites. The disappearance of respiratory enzyme precedes the dissolving of the cell structure, and it is possible to avoid this phenomenon by short recovery periods.

The respiratory enzymes are bound to membrane structures in the mitochondria (cristae mitochondriae). Spöndlin[16] by electronmicroscopy showed a breakdown of these membrane structures in the nerve endings and in the bases of hair cells following acoustic trauma; therefore, a recovery of the enzymatic activity is no longer possible.

Equally interesting as the ratio in the organ of Corti is the distribution of succinodehydrogenase in the ligamentum spirale. This enzyme is especially active in the epithelial cells of the stria vascularis. For many years it was believed that

the endolymph is originated from the stria vascularis. In earlier times it was assumed that similar to the perilymph production the vessels of the stria vascularis were also involved in the production of endolymph. The chemical properties of the endolymph differ from all other extracellular fluids, in that the concentration of potassiumions is much higher than the concentration of sodiumions[15]; therefore, it seems very unlikely that the endolymph is a blood filtrate, because this would require that somewhere the potassium must be separated from the blood plasma and the inflow of sodium must be prevented. These two functions can be achieved only by an active metabolic process. Only the epithelial cells in the stria vascularis are equipped for such an active metabolic process because of their content of respiratory enzymes.

Another area of the ligamentum spirale shows also considerable concentration of enzymes. This area is located behind the sulcus externus. Rather long processes of the epithelium have been observed in this area.[9] Some sections show that these extensions of the epithelial cells have been intensively stained by the indicator. Approximately 50 years ago Shambaugh[14] saw in these areas, gland-like canals which were lined with epithelium, and he believed that these epithelial cells also had secretory functions. It is very interesting that we found identical canals in our sections.

Not too many years ago Borghesan[1] showed that in these areas of the ligamentum spirale most of the blood vessels are concentrated, and he believed that the actual secretion of the endolymph takes place here and that the electrolytes were secreted in the stria vascularis. This conclusion is equally as difficult to prove as to disprove.

Histochemically it is known that the amplitude of the microphonics decreases when there is lack of oxygen. It is also known that the microphonics depend upon the presence of an endocochlear potential, and, finally, we know the relations between the content of potassium ions in the endolymph and the endocochlear potential.

Gisselsson[6] produced lack of oxygen by injecting potassium cyanide into the carotid artery thereby blocking the utiliza-

tion of the oxygen by inhibition of the respiratory enzymes. A short time after such an injection there is a decrease of the amplitude of the microphonics. Gisselsson believed that the respiratory enzymes in the hair cells would be inhibited by injecting potassium cyanide.[17] When we examine the experimental animals histochemically we find that the activity of the respiratory enzymes in the organ of Corti is unchanged or blocked in the stria vascularis. I believe, therefore, that histochemical methods supplement the physiological investigations of Davis,[2] Tasaki,[18] Misrahy,[10] and other investigators, on source of endocochlear potentials.

The properties of the endolymph and of the perilymph, especially their potassium and sodium content, has been known for a long time. During the last year we were very much interested in the investigations of Rauch,[11] who showed that the ratio of sodium to potassium in the fluid between the membrana reticularis and the basilar membrane is inversely related to the endolymph. These findings are definitely of great importance for the biology of the inner ear. On the other hand, we now know some facts about the chemistry of the stimulated nerve membrane of the peripheral nerve and the meaning of the potassiumion pump. We know that the energy for the potassiumion pump comes from ATP, and thereby forms cell respiration. One can, therefore, assume that sound-transformation in the inner ear follows a similar mechanism.

Answering the question raised in the beginning regarding the increase of energy during the transformation of sound, I should say that the histochemistry of the respiratory enzymes points to the fact that the main energy sources are located in the stria vascularis and in the sensory cells.

The stria vascularis, which has for many years been the battery of the endocochlear potential, shows histochemically the most intensive concentration of respiratory enzymes. According to Davis[3] the sensory cells modulate the endocochlear potentials. According to newly acquired knowledge of the properties of the fluid surrounding the hair cells, the sensory cells can perform this modulation by an exchange of ions, in

the same manner as it is done by the nerve cell. The abundance of respiratory enzymes in the sensory cells and in the nerve endings delivers the necessary energy.

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SIXTH INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST.

The Sixth International Congress on Diseases of the Chest will be held at the University of Vienna from August 29 to September 1, 1960.

INNERVATION OF THE COCHLEA IN RELATION TO HEARING LOSS.*†

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The report reviews briefly the present information regarding hearing loss associated with disorders of nerve supply of the cochlea, and considers the three following systems of fibers: autonomic, efferent and afferent.

A. The Autonomic Innervation.

The current knowledge about autonomic innervation of the cochlea and its physiologic correlates is fragmentary and often contradictory.

It is believed that the sympathetic innervation is represented by postganglionic fibers of the stellate ganglion. The fibers would follow successively the vertebral, basilar, anterior inferior cerebellar and internal auditory arteries. A supply of sympathetic fibers from the internal carotid artery and/or segmental contribution from other sources has been postulated.[1] Postganglionic fibers from the cervical ganglia reach the cochlear nerve via tympanic plexus, geniculate ganglion and facial nerve.[2]

The sympathetic fibers innervate the internal auditory artery and its primary and secondary tributaries situated in the modiolus. Arterioles and capillaries of both spiral lamina and spiral ligament including stria vascularis, seem to be entirely without innervation.[3,4] Studies of the stria vascularis by Smith[5] and Engström, et al.,[6] did not mention the presence of nerve fibers in its vascular bed.

The contribution of the parasympathetic division to the

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*Read at the meeting of the Middle Section, American Laryngological, Rhinological and Otological Society, Inc., Chicago, Ill., Jan. 18, 1960.

†Supported by Grant B-682 (C_3) from the U. S. Public Health Service.

Editor's Note: This manuscript received in The Laryngoscope Office and accepted for publication Feb. 8, 1960.

cochlea is unknown. Since Rasmussen[7,8] described the olivocochlear bundle it is quoted often that this represents a preganglionic parasympathetic innervation; however, this opinion seems untenable after further investigations by Rasmussen[9] and other authors.[10-14]

It is assumed that neurovascular disorders of the inner ear are associated with imbalance of the autonomic nervous system. The etiology of Ménière's disease and sudden deafness are attributed to arterial vasospasm of inner ear blood vessels. This theory has been elaborated and expanded despite little anatomical, physiological and pathological evidence.

The surgical procedures which aim to release the inner ear vascular supply from sympathetic action[15-25] in man, are not satisfactory. Little and sometimes contradictory results are reported on stimulation and ablation of the autonomic nervous system of the inner ear;[26,27,28] similarly, contradictory and often paradoxical results have been obtained with certain drugs which supposedly act upon the sympathetic and parasympathetic systems.[1,29,30]

There are several possible explanations for the failures and discrepancies in the surgical and experimental results mentioned above. The failure of the surgical procedure may, in some cases, be due either to the fact that the operation was performed in an irreversible lesion, or that the disorder was primarily not of autonomic origin. In other cases the failure may be caused by both incomplete denervation and sensitization. The clinical observations in sympathectomy in other organs[31] gave rise to two important conclusions which have a bearing on sympathectomy of the inner ear: first, in order to insure the result, the organ or structure must be denervated completely; second, to obtain maximal reduction of tone in arteries and minimal sensitization of the organ denervated, the sympathetic pathways must be interrupted at the preganglionic neuron.

The failure of sympathetic stimulation to induce physiologic and structural changes in the inner ear may be brought about by several factors. First as pointed out by Fulton,[32] the action of the autonomic nervous system varies considerably

from one species to another, and also among organs; furthermore, in the same organ the action varies according to the physiologic state of the tissue at the time of the experiment. Another important factor is that the internal auditory artery belongs to the central nervous system vascular supply which is known to be little affected by sympathetic stimulation.[33] Arteries larger than 50 microns show vasoconstriction of about 8 per cent, while there is no apparent change in smaller vessels. These factors must at least partially account for the results with drugs acting upon sympathetic and parasympathetic systems.

It is assumed that the autonomic imbalance may produce several degrees of vasoconstriction in the inner ear, but the corresponding functional and structural correlates are matters of much speculation. There are some experimental observations[34,35,36] supporting the opinion that if the autonomic imbalance produces arterial block, then a striking functional impairment must follow. In these experiments a mechanical temporary sudden block of the internal auditory artery in the guinea pig was produced. The blood flow of the capillary bed in the stria vascularis was used as an index of complete obstruction. Cochlear potentials were observed and measured before, during and after the arterial block. The survival time of neural components was about 45 seconds while that of aerobic cochlear microphonics was twice as long. The revival of cochlear function was related to duration of the occlusion. Complete recovery may occur after a blocking of no more than 30 minutes; between 30 and 50 minutes the recovery was partial and a permanent depression followed an occlusion of 60 minutes or more. The latter produced severe and irreversible changes in sensory hair cells and afferent neurons.

These experimental observations strongly suggest that some human cases of sudden deafness may be due to occlusion of vascular supply; however there is little evidence whether the condition is brought about by vasospasm, embolus or other mechanisms.

The extensive literature on the anatomy, physiology and physiopathology of autonomic nervous system of the inner

ear can be found in the comprehensive work of Montandon,[1] Williams,[25] Bocca[37] and others.[38,39]

B. The Efferent Innervation.

Rasmussen[7,8,9] demonstrated that the crossed limb of the so-called olivary peduncle originating in the superior olivary complex enters the cochlea of the opposite side. This olivo-cochlear bundle passes into the inner meatus between superior and inferior division of the vestibular nerve; it reaches as far as the saccular ganglion, and crosses toward the cochlear nerve forming the fasciculus of Oort. The fibers enter the cochlea by two or three fasciculi which run along the cochlea as a spiral intraganglionic bundle.[3,9,10,11,40] The observations indicate that not all components of the spiral intraganglionic bundle are efferent fibers; some of them probably belong to the afferent innervation.[3,9] Rasmussen[9] suggests that in addition to the olivo-cochlear bundle other efferent systems to the cochlea may exist.

The nerve endings of the olivo-cochlear bundle still remain unknown although some authors[10,11,12] proposed that the bundle innervates the internal hair cells; however, recent investigations[38,41-45] suggest that the olivo-cochlear bundle innervates both inner and outer hair cells. The bundle seems to represent the final pathway of a descending system which extends from the cortex to the cochlea.[46] The system makes synaptic connections with many and probably all auditory nuclei. According to Galambos,[46] activation of the descending system may represent a neural mechanism acting as modulator of the incoming auditory signals. So far, his experimental observations show that activation of the olivo-cochlear bundle inhibits the cochlear neural components. The mechanism of this phenomenon and its effect upon hearing in normal and pathologic conditions are still speculative matters.

C. The Afferent Innervation.

In man the cochlea is innervated by about 35,000 afferent neurons.[47,48] The central axons terminate in the primary cochlear nucleus.[49,50,51] The dendritic processes are distributed among 23,000 sensory hair cells in the organ of Corti. The

anatomical pattern of nerve fibers among hair cells have been described by several authors (von Ebner,[52] Ramón y Cajal,[53] Held,[54] Lorente de Nó,[3] Polyak,[55] and others). The internal hair cells are innervated mainly by radial fibers while the external hair cells are supplied by spiral fibers. The latter extend considerably along the organ of Corti. The radial fibers innervate one or a few sensory cells while many hair cells are innervated by one spiral fiber. The electron microscope shows two types of nerve endings on the sensory hair cells,[38,43,44] large and small terminations containing more or less granules or vesicles. The question whether one corresponds to an afferent nerve and the other to an efferent fiber has not been settled. The density of afferent neurons along the ganglion of Corti is uniform except at both the basal and apical end of the Rosenthal's canal, where the density is diminished.

The significance of this multiple innervation is unknown. The evidence from human material and experimental animals, however, suggests that this multiple innervation is not necessary for coding auditory signals of simple nature such as threshold of pure tones. Dandy[56] reported that section of as much as two-thirds of the cochlear nerve in some cases of Ménière's disease, did not modify significantly the pre-operatory audiometric thresholds. In other cases the section produced a small or pronounced threshold shift, mainly for high frequencies.

Several investigations in laboratory animals[57-61] revealed that an atrophy of as much as 75 per cent of neurons may be associated with thresholds within normal limits. Schuknecht and Woellner[60] showed in the cat that nerve degeneration localized at the basal coil produced larger threshold shift (high frequencies) than that arising from a lesion of similar magnitude localized at the apex (low frequencies). The explanation may be due to basalward spread of the response-area for low frequencies as intensity of stimulus increases.

The multiple cochlear innervation, however, seems to be necessary for recording complex auditory signals, such as speech or even loudness of a simple tone. Loudness seems to

be a function of the total number of nerve impulses per unit time. This is determined by the number of fibers activated and number of nerve impulses in each fiber. Since the latter is limited by the refractory period it is apparent that the number of fibers activated is critical for carrying loudness function; thus, a diminution of neurons will be associated with impairment of loudness function. It is known that diseases involving only the cochlear nerve generally present no recruitment while this is associated with lesions of the sensory cells. Dix[62] reported two cases of acoustic neurofibroma presenting loudness recruitment which disappeared after surgical removal of the tumor. This finding was attributed to impairment of sensory cell function resulting from decreased vascular supply. This explanation is questionable because impairment of circulation should affect nerve cells equally if not more strongly than sensory hair cells.

The multiple innervation seems to play an important role in coding speech. Lesions affecting the cochlear nerve, such as acoustic neurinoma, and presbycusis of "neural atrophy" type produce severe loss in auditory discrimination.

SUMMARY.

The mammalian cochlea is innervated by three systems of fibers, *ie.*, autonomic, efferent and afferent.

There is little evidence that imbalance of the autonomic nervous system produces vascular disorders resulting in hearing loss. The theory of vasospasm as a manifestation of autonomic imbalance requires a thorough investigation.

The information about the efferent system is still fragmentary. It is not known whether and how disorders of this system affect hearing function.

The significance of multiple innervation in the cochlea is unknown; however, for coding auditory signals of simple nature, such as pure tones at threshold, it is not necessary. Several observations in man and animals revealed that a large reduction of nerve population is compatible with thresholds within normal limits. On the other hand, coding of

complex auditory signals such as loudness function and speech, requires integrity of cochlear innervation. A typical example is absence of loudness recruitment and severe loss of auditory discrimination associated with an acoustic neurinoma.

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ANNUAL OTOLARYNGOLOGIC ASSEMBLY.

September 24-30, 1960.

The University of Illinois College of Medicine Department of Otolaryngology will offer an intensive postgraduate basic and clinical program for practicing otolaryngologists. The Assembly offers a compact program of one week of daytime and evening sessions. It is designed to bring to specialists a wide variety of current advances in management, therapy and philosophies. Review of basic morphologic features is also included by means of laboratory demonstrations, dissection and prosection, all augmented by visual aids.

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Interested physicians should write direct to the Department of Otolaryngology, University of Illinois College of Medicine, 1853 West Polk Street, Chicago 12, Ill.

CLINICAL IMPLICATIONS OF RECENT RESEARCH ON THE INNER EAR.*†

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Recently I have been doing some worrying about two distantly related problems. The first was the technical problem of relating changes in electrophysiological responses from the cochlea of the guinea pig following acoustic trauma to the anatomical changes that Dr. Walter Covell and I could see in the microscopic sections of the same cochleas. The second problem was, "What guides do we have for the causal relations between exposure to noise and loss of hearing?" The latter question became especially important in Missouri with the enactment of new sections on Occupational Hearing Loss in the Missouri Workmen's Compensation Law.[1]

I plan to suggest that the evidence arising from the technical problem should help the clinician to divide the problem of causal relations into more manageable packages. This by no means solves the whole problem of causal relations, but I believe it will help to mark off two extreme areas of greater certainty from a middle area of great *un*certainty. In general outline the hypothesis is not new. I will suggest that acoustic trauma can be considered to depend upon a pathologic physiology that is different from that of noise-induced hearing loss. I should emphasize here that I do *not* use the terms "acoustic trauma" and "noise-induced hearing loss" synonymously. I believe acoustic trauma to be an acute process, more truly traumatic, and noise-induced-hearing loss to be a chronic process that is not, strictly speaking, traumatic. Under certain

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*Read at the meeting of the Middle Section, American Laryngological, Rhinological and Otological Society, Inc., Chicago, Ill., Jan. 18-19, 1960.

†Supported in part by Grant B-1710 from the National Institute of Neurological Diseases and Blindness to Central Institute for the Deaf. Reproduction is permitted for any purpose of the United States Government.

Editor's Note: This manuscript received in The Laryngoscope Office and accepted for publication Feb. 8, 1960.

extreme but common conditions of exposure to noise we can exclude one or the other of the two processes. Whenever these conditions are met, I believe the possibilities to be considered with respect to causal relations are greatly simplified.

STATUTORY OCCUPATIONAL LOSS OF HEARING.

The expert testimony of the otolaryngologist is usually required to establish the hearing status of the claimant and also to establish the cause of any defective hearing. To demonstrate the problem I will refer to the new statutes for Missouri. Other statutes may differ in detail, but the general problem is universal. In Missouri the pertinent paragraphs of statute to be implemented by testimony begin as follows:

"An employee shall be conclusively deemed to have been exposed to the hazards of an occupational disease when for any length of time, however short, he is employed in an occupation or process in which the hazard of the disease exists."

The next paragraph is legally complex but concludes:

". . . . and, in such cases," (silicosis, asbestosis, loss of hearing due to industrial noise, and radiation disability) "an exposure during a period of less than ninety (90) days after the effective date of this section shall be held not to be a last exposure."

The paragraph implies that the named occupational diseases are not immediately manifest upon exposure but require at least ninety days for an significant manifestation.

Occupational disease is defined both by exclusion and by inclusion in another section.

". . . . ordinary diseases of life to which the general public is exposed outside of the employment shall not be compensable, except where the said diseases follow as an incident of an occupational disease as defined in this section. A disease shall be deemed to arise out of employment only if there is apparent to the rational mind upon consideration of all the circumstances a direct causal connection between the con-

ditions under which the work is performed and the occupational disease, and which can be seen to have followed as a natural incident of the work as a result of the exposure occasioned by the nature of the employment as the proximate cause, and which does not come from a hazard to which workmen would have been equally exposed outside of the employment."

Finally, we have in the next paragraph:

"Loss of hearing due to industrial noise is recognized as an occupational disease for the purposes of this chapter and is hereby defined to be a loss of hearing in one or both ears due to prolonged exposure to harmful noise in employment. Harmful noise means sound capable of producing occupational deafness."

This definition of harmful noise makes a closed circle in only two sentences. This is little help for the expert witness. To a very considerable degree he must have his own responsible opinion in each case. The statutes could not be written to define a harmful exposure to noise more accurately because enough information to write a good statute simply is not available. Accordingly the wisdom of the otolaryngologist must be substituted for the information that is not available.

ACOUSTIC TRAUMA IN THE GUINEA PIG.

The past history and present problems of experiments in acoustic trauma on the guinea pig[2,3,4,5,6] and other laboratory animals now seem to provide some clues that may fortify the otologist's wisdom. The comparisons I make to man can only be qualitative. This is because I believe the ear of the guinea pig to be 20 db to 25 db more sensitive to noise than the ear of man.

If I expose the ear of the guinea pig for one to four minutes to a tone in excess of 140 db SPL and examine the ear a few days later, the destruction seen at the site of worst injury is often complete. A few scattered fragments of cells of the organ of Corti are apparent, but a low epithelium will have replaced the familiar structures.

If the exposure is reduced to 140 db for the same duration, the worst injury is still very great, but enough of the supporting cells may remain in place to preserve a recognizable structure. Reissner's membrane may be broken. The rods of the tunnel of Corti may be fractured, allowing collapse and fracture of the reticular lamina. The hair cells are usually pretty well destroyed. No definite cochlear microphonic (CM) can be recorded from such areas. Occasionally one may record CM from adjacent less injured areas.

When the exposure is reduced to about 135 db and lasts a few minutes, rather than one or two, the overall structure of the organ of Corti is even better preserved. Occasionally there may be rupture of Reissner's membrane, but usually the tunnel of Corti and the reticular lamina remain intact. Many of the hair cells and their Deiters' cells will be severely injured. Often, but not always, there will be enough intact cells to give a small CM. Adjacent areas are less severely injured and may yield fairly good CM.

The character of the worst injury changes again for exposures to 125 db lasting from 20 to 30 minutes. Here we may find hair cells normal or almost normal in appearance, but Deiters' cells may be rather badly broken apart. Pieces of these cells may even be seen scattered in the tunnel of Corti. The threshold for a three microvolt CM response from one of these areas may be elevated 50 db; however, the cells do give a true response that may grow to considerable voltages with strong test tones.

Throughout the sequence that I have been tracing, the sound pressure level for each successive example has been reduced. Longer exposures were required for the lower sound pressures in order to produce visible injuries. All exposures clearly injured the ears but the *character of the worst injury in each ear changed progressively.* Now, if we reduce the sound pressure level to about 115 db and increase the duration of the exposure to about two hours, the anatomic changes become even less pronounced. Some small lesions involving hair cells and supporting cells occur. There are small to moderately large losses in CM and in the nerve action potentials (AP) recorded

from these ears. Unfortunately, the degree of loss of cochlear potentials does not regularly match the severity of the injuries seen under the microscope. Too often substantial losses of cochlear potentials are paired with a relatively undisturbed organ of Corti. Similarly, an organ of Corti that shows a moderate number of apparently injured hair cells may show very little loss of cochlear potentials. These contradictory relations appear whether the ear specimens are taken immediately after exposure or not until three months after the the exposure.

The evidence that the hair cells are the source of cochlear microphonics is so overwhelming that we can only conclude that the usual histologic techniques of examination are not adequate to evaluate these injuries properly. I personally believe that some of the newer histochemical methods, such as those described by Dr. Vosteen, and the electron microscope will help us to understand why. For the discussion here, however, it is the changing nature of the injuries that is important and should be remembered.

NOISE-INDUCED HEARING LOSS AND ACOUSTIC TRAUMA.

In man we know noise-induced hearing loss and acoustic trauma much better by the threshold shifts produced than we do by the details of the pathology of the organ of Corti. I like to reserve the term "acoustic trauma" for the permanent threshold shift and injury that follows either a single exposure to an explosive episode or a brief exposure to high level noise. The constant feature of the environment is the presence of peak sound pressures in excess of 135 db SPL. It does not matter whether these peaks are impulsive or occur in a continuous noise. By analogy to the experiments on the guinea pig, acoustic trauma should really include any exposure that immediately and directly injures cells of the organ of Corti. In man there is characteristically a rather large threshold shift, most of which is temporary.

I would like to use the term "noise-induced hearing loss" for the losses that are observed only following years of exposure to relatively steady machinery noise. The overall

levels may be about 105 db SPL and the levels in the octave bands from 300 cps to 2,400 cps are usually between 85 db and 95 db. Such noises are relatively intense compared to noises encountered in everyday life.

The threshold shift that follows exposure for a single day to these noises is temporary. Recovery is apparently complete. For some people recovery from these exposures is always complete even after a lifetime of repeated exposure. From these observed relations I infer that these exposures do not produce a direct, permanent anatomic injury. The functional defect is more likely to be of the nature of a temporary biochemical depletion of necessary metabolites, the temporary accumulation of toxic by-products of metabolism, or temporary physical distortions that require metabolic activity for restoration. Some ears, however, eventually fail to recover if these exposures are repeated, and develop a permanent threshold shift. From this we infer that the repetition of the temporary functional defect can lead to anatomical degeneration. The end result may not differ materially from that produced by acoustic trauma, but the processes that lead to the result differ significantly.

Even though I have emphasized the differences between acoustic trauma and noise-induced hearing loss I do not at all mean to imply that they are necessarily mutually exclusive processes. They surely can both be present in the same ear. I emphasize the differences because whenever we have reason to believe that only one of the processes is present we can better understand the events that could have taken place within a particular ear.

DISCUSSION.

In this discussion I shall be concerned primarily with several hypothetical patients presenting permanent threshold shifts following some kind of exposure to noise. The hearing is presumed, *but not definitely known,* to have been normal prior to exposure. The usual medical conditions producing threshold shifts have been ruled out. The question that remains is, "Could the threshold shift have been produced by the reported

exposure to noise, or is it much more likely to be a threshold shift of unknown etiology that would have been present in the absence of the exposure?" The answers I am giving are consistent with the general scheme I have been developing and represent my own opinions based on this scheme.

First, let us consider exposures to steady continuous noise without unusual pressure peaks. The sound pressure level in the octave bands 300 cps to 2,400 cps may equal but on the average not exceed 95 db. A casual visitor spends the better part of a day in the work area. On leaving he complains of tinnitus and later appears with a permanent threshold shift. Or an electrician has been installing new wiring in the general work area for a week. Regular production and noise schedules have been maintained. The electrician complains that the noise is "deafening" and later appears with a permanent threshold shift. These have both been relatively short exposures to the kind of noise we associate with noise-induced hearing loss and not with acoustic trauma. The exposure to noise should not be considered responsible for their threshold shifts even if we assume these ears to be especially sensitive to noise. I believe an otologist can fairly testify that these exposures could not possibly be causally related to the threshold shifts.

If we consider the case of a regular employee who has been on the job three months to a year, the problem is somewhat more difficult. We do know that some individuals are more sensitive to noise than others and must accept the *possibility* that this exposure could be responsible for a very small permanent threshold shift. A large threshold shift would be distinctly unreasonable. Accordingly, the larger the threshold shift, the more certain it is that the exposure to noise was not responsible. We expect a small percentage of regular employees to show large permanent threshold shifts at 4,000 cps and modest threshold shifts for lower frequencies after five or more years of exposure for eight hours a day. Without other evidence from prior audiometry one would have to testify that such exposures could have produced the threshold shifts.

Now let us jump to a set of exposures that we may expect to produce acoustic trauma. This kind of sound field will commonly include impulsive or explosive noises with peak pressures that regularly exceed 135 db SPL. The larger drop forges, jet engines and gunfire are three examples of sources for this kind of noise. Under these circumstances it is possible, *but not common*, for our casual visitor to show a large temporary threshold shift with a small permanent residual. If the equivalent of the electrician is assumed to have sensitive ears, he also may show some permanent threshold shift that can be attributed to his exposure. The possibilities for regular employees are obvious. Even so, many persons will not show permanent threshold shifts until they have been exposed for years.

The rules I have been using for the above cases are not so helpful for the range of exposures from 95 db per octave band to frequent peaks of 135 db. In this range we must assume the possibility that the acute processes of acoustic trauma and the chronic processes of noise-induced hearing loss can be present together. One useful generalization is possible. These sound pressures are not great enough to produce acoustic trauma unless the exposures last for several hours. Accordingly, it should not be possible for one or a few 15-minute exposures to peak pressures of 125 db to be responsible for a permanent threshold shift. There will be many other combinations of duration and level of exposure that are universally safe, but most of these are harder to identify with certainty. Under these circumstances statements about the possibilities for causal relations are less positive and a larger element of judgment is required.

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INTERNATIONAL POSTGRADUATE COURSE IN RECONSTRUCTIVE SURGERY OF THE EXTERNAL NASAL PYRAMID AND NASAL SEPTUM.

An international course in Reconstructive Surgery of the External Nasal Pyramid and Nasal Septum will be given in Mexico City July 4-15, 1960, under the auspices of the University of Mexico Medical School and its Postgraduate Department, in cooperation with the American Rhinologic Society, and under the direction of Dr. Andres Bustamante Gurria, of Mexico City. The guest professor will be Dr. Maurice H. Cottle, Chicago Medical School. He will be assisted by a faculty of otorhinolaryngologists from the United States and Mexico.

Class membership is limited. Apply for registration information to Dr. Robert M. Hansen, Secretary, American Rhinologic Society, 1735 North Wheeler Ave., Portland 17, Ore.

HISTOPATHOLOGIC INNER EAR CHANGES IN DEAFNESS DUE TO NEOMYCIN IN A HUMAN.*†‡

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The toxic effect of certain antibiotics on the sense organs in the inner ear has caused concern since streptomycin first came into clinical use. The known offenders have been streptomycin, dihydrostreptomycin, neomycin and kanamycin, all of which belong to the "useful but unruly family of basic streptomyces antibiotics."[1]

This concern has been recently intensified with the increasing incidence of ototoxicity following relatively small doses of these drugs. The widespread use of dihydrostreptomycin in combination with other antibiotics as recently reported by Shambaugh, et al.,[2] undoubtedly has been related to this increase. The common occurrence of hearing impairment and often severe deafness after prolonged administration of these drugs with high dosage has been well documented (Streptomycin,[3,4,6,7,8] Dihydrostreptomycin,[2,5,7,8,9,10] Neomycin,[11,12,13,14,15,16,17] Kanamycin[1,18]). The toxicity of streptomycin for the vestibular system as compared with the auditory system has been generally recognized. In contrast, dihydrostreptomycin, neomycin and kanamycin has shown greater toxicity for the auditory system. A greater tendency to ototoxicity in the

*Read at the meeting of the Middle Section, American Laryngological, Rhinological and Otological Society, Inc., Chicago, Ill., Jan. 18, 1960.

†From the University of Chicago Medical School and the University of California Medical School.

‡This work has been aided by a grant from the Central Bureau of Research of the American Otological Society, Inc.

Editor's Note: This manuscript received in The Laryngoscope Office and accepted for publication Feb. 8, 1960.

presence of high blood concentrations has been reported by certain authors,[1,11,12,15,19,20,21] but denied by at least one author.[22]

A toxic effect on the kidney has been reported from neomycin and kanamycin,[1,15,23,24,25] but less frequently from dihydrostreptomycin and streptomycin.[26,27,28] This has been thought to be a factor in increasing the blood levels and the tendency to ototoxicity.

In recent years cases of auditory damage have occurred after a low total dosage of these drugs, administered within several days only.[1,17,29,30] Impaired renal function has been evident in some of these cases, but is not known to have existed in all.

Onset of the hearing impairment as long as one month after cessation of therapy has been noted in many instances[1,5,9,10,22] and has been reported after as long as five months.

The toxic effect of these drugs on the cochlear and vestibular systems in animals has been well demonstrated. Pathologic changes in the cochlear nuclei in dogs and in the vestibular and cochlear nuclei in humans were reported by Stevenson, et al.,[31] from streptomycin. Winston, et al.[32,33] reported changes in the cerebellar cortex, medial and lateral vestibular nuclei and other areas in the brain stem of cats from streptomycin. Christensen[34,35] reported degeneration in the central vestibular and cochlear nuclei after streptomycin in chronic experiments in guinea pigs. Floberg, et al.,[36] reported inhibition of intracellular production of nucleic acids in vestibular nerve cells and Deiters' nucleus.

Degenerative changes in the peripheral receptor organs in animals have been demonstrated by Causse,[37] Berg,[38,39] Ruedi,[40,41,42] Hawkins and Lurie,[43] Hawkins, et al.,[1] Schuknecht,[44] Riskaer,[45] and Nakamura;[46] also less marked ascending degenerative changes in the nerve have been described.[34,35,36,37,38,39,40,42,43,45,46] Atrophy and degenerative changes in the stria vascularis have been reported in several,[40,41,42,45,46] but were not noted in other reports.[37,43] Loss of auditory function also has been confirmed by recording of the electric potentials.[1,42,43,46,47]

In the human, atrophy of the sensory cells in the organ of Corti was first demonstrated in 1951 by K. Graf[48] in cases of tuberculous meningitis, which became deaf during streptomycin therapy. No other definitive description of histopathologic changes in the sensory receptors in the human ear due to antibiotics has been found in the literature. Temporal bones from human cases of tuberculous meningitis were also examined by Whetnall and Lucas,[49] but they did not permit a differentiation between the inflammatory effects and possible drug toxicity.

The present report presents histopathologic findings in a human which followed neomycin therapy. The case report is as follows:

The patient (H.K.O.) was a 50-year-old white male who was receiving treatment for subacute bacterial endocarditis. When first hospitalized he received five million units of penicillin and one gram of streptomycin daily by injection for four days. Blood culture grew aerobacter aerogenes which were inhibited by less than 10 micrograms per cc. of neomycin and less than five milligrams of polymixin B. Fifty milligrams of polymixin B was given daily by injection for seven days and ½-gram of neomycin was given concurrently twice daily by injection and continued for 19 days, except for two days when he received ½ gram daily.

Although no hearing loss had been noted following the streptomycin therapy, it was now discovered that the patient was completely deaf. No dizziness was present, although the patient was nauseated and vomited on two or three occasions.

There was no history of disease of the ears, nose, or throat, and on entry into the Armed Services on June 24, 1942, the patient had had 20/20 hearing bilaterally. Examination on December 6, 1957, revealed grossly complete deafness and otherwise essentially normal ears, nose and throat. A caloric test employing 40 seconds of irrigation with 50 cc. of water at 40° C. produced nystagmus directed away from the tested ear with a duration of two minutes and 30 seconds for both ears.

AUDIOGRAM—December 13, 1957.

	125	250	500	1000	2000	4000	8000
Right Ear	NR	NR	90	95	NR	NR	NR
Left Ear	NR	65	85	90	80	90	NR

Bone Conduction: No response at any frequency.

Speech Detection: Right ear 90. Left ear 80.

The patient expired on February 12, 1959, at 1:00 P.M. The temporal bones were removed the following day and placed in 10 per cent Formalin. Decalcification and mounting of the specimen were carried out in the routine manner.

HISTOPATHOLOGICAL FINDINGS.

Left Ear. Labyrinthine Capsule and Middle Ear Spaces. The left temporal bone was in a good general state of preservation. The mastoid was well pneumatized, with a tract of large air cells extending posteromedially to the labyrinth as far as the internal meatus. No inflammatory or other changes were present in the middle ear, mastoid, or internal acoustic meatus.

Fig. 1. Microphotograph X580, showing organ of Corti, left side, at junction of upper and middle coil. The inner hair cell is absent. Outer hair cells show a combination of postmortem degeneration and toxic effects. The outer pillar shows partial degeneration. Depression of Reissner's membrane was localized and probably artifact.

Inner Ear. There were early post mortem degenerative changes of mild degree affecting the receptor organs. These, however, were not great enough to obscure the pathologic changes to be described. The vestibular sensory epithelium showed no changes which were not attributable to early post mortem degeneration. The vestibular nerve fibers and Scarpa's ganglion appeared normal.

The organ of Corti showed an absence of the inner hair cell which was nearly complete throughout (see Fig. 1). Only an occasional cell remained. The outer hair cells also showed degeneration throughout, but of lesser degree. The estimated

percentage of degenerated cells varied from 100 per cent to about 60 per cent. The distribution of the degeneration was irregular. Areas of maximum loss were found both in the apical coil and in the basal coil.

The pillars also showed degenerative change. In limited areas both in the apical and basal coils the external pillar was absent or markedly degenerated, while in some areas it showed

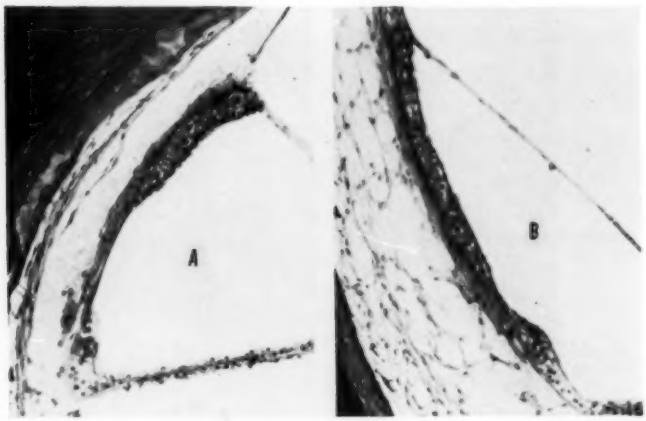

Fig. 2. Microphotographs X225 showing the stria vascularis in the apical coil A, and in the middle coil B of the left ear. The stria in A is considered as partially atrophied, but normal in extent in B. The condition varied throughout the cochlea with A representing the extreme degree of loss.

little definite change. The inner pillars showed a lesser degree of change than the outer.

The stria vascularis was present throughout. In some areas it was absent immediately above the spiral prominence for one-third or more of the distance to Reissner's membrane (see Fig. 2). In other areas it extended down to the spiral prominence. The peripheral cochlear neuron and the spiral ganglion appeared normal throughout. Distortions of Reissner's membrane, the tectorial membrane and the inner pillar were present which can be ascribed to fixation artifact.

Some loss of Deiters' cells was evident in areas where degeneration of pillars was most marked.

Hensen's cells and the outer and inner sulcus cells were relatively well preserved.

Right Ear.

The labyrinthine capsule and middle ear spaces were normal throughout. Pneumatization was extensive in the area posteromedial to the labyrinth. The internal meatus was round.

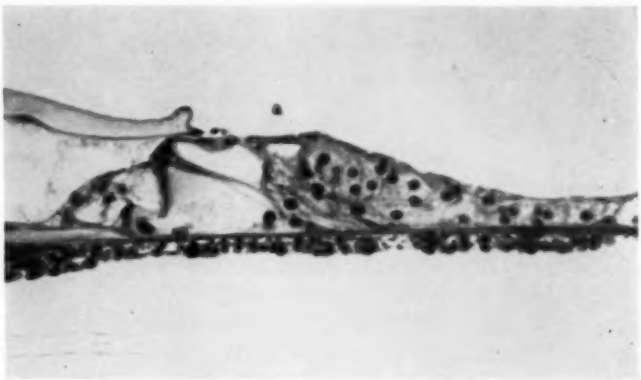

Fig. 3. Microphotograph X580, right cochlea, section through the junction of middle and basal coils. The inner hair cell is absent. Outer hair cells are mostly degenerated. The pillars show early degenerative changes at their bases.

Inner Ear.

The state of preservation corresponded to the left ear. Early post mortem degenerative changes were present but could usually be distinguished from toxic degenerative effects. The vestibular receptor organs were well preserved and showed no evidence of toxic change. The nerves and ganglion cells appeared normal.

The organ of Corti showed changes which were almost identical with the left ear. The inner hair cells were almost all absent. The degree and distribution of degeneration of

outer hair cells, pillars and Deiters' cells corresponded fairly well to the opposite side (see Fig. 3). In one area at the beginning of the apical coil (see Fig. 4) the inner and outer hair cells, and the outer pillar were absent. In the middle part of the basal coil, the inner and outer hair cells, the pillars and Deiters' cells and Hensen cells all showed much degeneration (see Fig. 5). The peripheral cochlear neurons were well preserved.

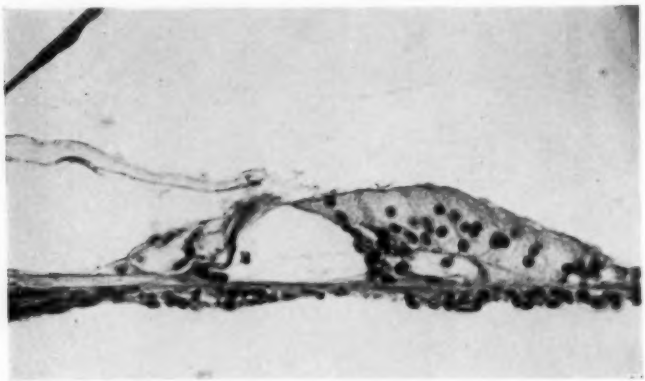

Fig. 4. Microphotograph X580, right ear, showing organ of Corti at junction of apical and middle coils. The inner hair cell is absent. Outer hair cells are absent except for possible remnants. The outer pillar is absent and the inner pillar degenerated. Deiters' cells are seen only as distorted remnants.

Reissner's membrane was depressed in some areas, as on the opposite side and the tectorial membrane and inner pillar showed the distortion typical of fixation artifact.

SUMMARY OF HISTOPATHOLOGIC FINDINGS.

The degenerative changes which are of significance are similar in the two ears, but more advanced in two particular areas on the right (see Figs. 4, 5).

An estimate of the percentage loss of hair cells throughout indicated a slightly greater loss of both inner and outer cells on the right. The distribution of loss was similar in that it

was irregular, but the loss of the inner cells on the right was almost total.

The outer pillar showed greater degenerative changes than the inner. The loss of pillar cells was less marked than loss of hair cells. Deiters' cells showed less degeneration than the pillars.

The stria vascularis might be interpreted as showing some degree of atrophy in some areas (see Fig. 2), but it is un-

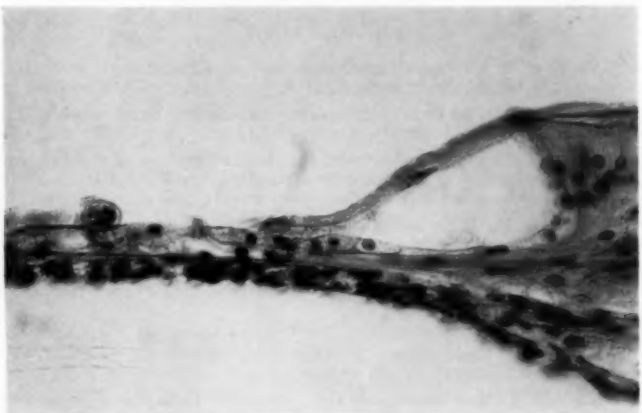

Fig. 5. Microphotograph X580, right cochlea, section through the middle part of the basal coil, showing advanced degeneration of hair cells, pillar cells, Deiters' and Hansen's cells.

likely that this was of functional significance. There was no evidence that changes in the stria were locally related to toxic degeneration of the hair cells.

DISCUSSION.

In reviewing the history of this case, the total dosage of streptomycin (four grams in four days) and of polymixin B (50 milligrams per day for seven days) could not be considered the cause of deafness. The dosage of neomycin, 18 grams in 19 days, definitely appears to have been responsible.

The toxic effect of the drug on the inner ears in this case has been evidenced mainly by degeneration of the inner hair cells, and to a lesser extent, the outer hair cells. Lesser degrees of degeneration were evident in the pillars, and to a minor degree in Deiters' cells. While it is not possible to exclude a toxic effect on the cochlear nuclei and central pathways in this case, it is perhaps significant that the peripheral cochlear neurons were well preserved. The degree of degeneration of the hair cells and to a lesser degree of the supporting cells provides an adequate explanation for the loss of hearing.

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REVERSIBLE HEARING LOSS IN HUMAN HYPOTHYROIDISM AND CORRELATED CHANGES IN THE CHICK INNER EAR.*†

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Deafness has been associated with disease of the thyroid gland by many observers, and although this deafness has generally been reported as of the perceptive type, the exact cause has not been demonstrated. One of the reasons for this is that the changes associated with hypothyroidism depend upon whether the thyroid failure occurs during the embryonic development of the individual or occurs at later stages in life.

The congenital type of hypothyroidism results in cretinism in which deafness is most frequently found. This deafness is progressive throughout life and usually ends in total loss of hearing.[1,2] Although cretinism seems to cause a perceptive deafness there has not always been support for this view. Nager[3] in reporting the histology of the cretin temporal bone describes it as smaller than normal with marked hyperostosis on the medial wall of the cavum tympani which leads to narrowness and occlusion of the window niches. The ossicles are deformed and enlarged, but there are only slight changes in the organ of Corti. On the basis of this anatomical evidence the deafness would appear to be conductive rather than perceptive.

Deafness has also been observed in acquired hypothyroidism.

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*Read in part at the meeting of the Middle Section of the American Laryngological, Rhinological and Otological Society, Inc., Chicago, Ill., Jan. 18-19, 1960.

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Editor's Note: This manuscript received in The Laryngoscope Office and accepted for publication Feb. 8, 1960.

Howarth and Lloyd[4] record five such cases. Barnes[5] treated cases of hypothyroidism and associated deafness, noting hearing improvement in many instances. Moehlig,[6] McLaurin,[7] and Barlow[8] have also reported deafness as occuring in cases of hypothyroidism. The deafness in these cases does not seem to be as severe as that in cretins, and the evidence for either a conductive or perceptive type of lesion is no clearer.

According to McMahon[9] the deafness may be conductive, if edema of middle ear or Eustachian tube is present; or perceptive from some obscure effect of lack of thyroid on the inner ear. Marquet[10] states that the auditory disturbances appear late in hypothyroidism and can be attributed to intercellular edema of the tissues. Both middle ear and labyrinthine lesions occur. In the latter, the membranous labyrinth shows sclerotic changes and the cuboidal epithelial cells become atrophic. These are found in the vestibule and constitute examples of atypical degeneration. He further cites four causes of this deafness: *1.* a congenital process similar to that of hereditary labyrinthine deafness, *2.* lesions of the osseous capsule of the labyrinth (edema and possibly hemorrhagic suffusions), *3.* blockage of the two windows and *4.* true intralabyrinthine hypertension based on myxedematous infiltration affecting the endolymphatic circulation.

It appears then, that the aural anatomical changes present in thyroid disease vary with the degree of the disease present, and it is conceivable that slight changes in hearing could occur with subtle changes in thyroid activity; furthermore, from the reports, it seems that the changes in hearing can occasionally be reversed upon treatment of the hypothyroidism.

Two cases of hypothryoidism and associated hearing loss have recently been seen in the University of Michigan Otology clinic. These have been carefully examined audiometrically to determine whether the deafness is conductive or perceptive. The hearing was followed in each case after treatment. Following this clinical and audiometric study, an experiment was set up to see whether the anatomical locus of changes producing the hearing loss could be determined. Because of the ease with which developing chick embryos can be made hypo-

thyroid the studies were made on the developed chick ear even though it anatomically is somewhat different from the human.

CASE REPORTS.

Case 1. Mr. R.C., a 52-year-old male, was known to have had hypertension 17 years prior to admission to the University Hospital in February, 1959. Five years prior to admission he had a severe chest pain with a diagnosis of a myocardial infarction and at that time he was placed on potassium thiocyanate, four tablets daily. This dosage was maintained for two years, then decreased to three tablets daily and more recently, prior to admission in February, 1959, to two tablets daily. In November, 1958, he had noticed decreased hearing and gradual enlargement of his thyroid gland. Concomitantly, he noticed also puffy eyelids and a dry skin.

Examination in February, 1959, showed a blood pressure of 105/70, and a pulse of 84. The skin was dry, warm, and doughy. The thyroid gland was found to be diffusely enlarged without nodules or tenderness. He was referred to the ear, nose, and throat clinic where the additional history of nine years' work in a very noisy environment was obtained. The examination of the ears, nose and throat was essentially within the limits of normal, except that the nodular thyroid was also noticed. Audiograms shown in Fig. 1-a reveal a perceptive hearing loss. The average loss for the speech frequencies in the left ear was approximately 25 decibels and in the right ear approximately 35 decibels. There is a decrease in sensitivity to the high frequencies typical of a noise induced hearing impairment. A discrimination loss was recorded at 48 per cent in the right ear and 36 per cent for the left ear.

The laboratory findings showed normal urine and blood picture. A BMR was found to be minus 23 per cent; serum cholesterol 220 mg. per cent, PBI 1.6 gamma per cent, and the 24 hour iodine 131 uptake was 9.8 per cent. The serum thiocyanate was 11 mg. per cent. These findings as recorded on February 24, 1959, were consistent with hypothyroidism.

The patient was taken off his thiocyanate and treated with digitalis and dicoumarol because of his heart disease and was discharged on March 7, 1959.

He was readmitted March 15, 1959, because of chest pain, cough and fever of 101.6° F. In the interim, he stated that he had been feeling much better and that his appetite and hearing had improved. Examination showed the thyroid to be slightly enlarged as before.

Audiograms were again taken and are shown in Fig. 1-b. There is a marked improvement in his hearing. The bilateral perceptive hearing loss for the high tones, specifically in the region of 4,000 and 8,000 cps persists, but for the speech frequency of 1,000 cps the loss is only 5 decibels.

Laboratory findings on March 19, 1959, showed a 24 hour iodine uptake of 43.6 per cent which was interpreted as showing a low hyperthyroid range of uptake compatible with a gland which has been previously depleted of thyroid by potassium thiocyanate and is now enjoying a rebound hyperthyroid uptake following the withdrawal of the potassium thiocyanate. In addition, the serum cholesterol was now 187 mg. per cent, thiocyanate 2.2 mg. per cent, and the PBI 5.2 gamma per cent. These findings, recorded on March 26, 1959, are within the limits of normal.

It is the impression that this is a case of hypothyroidism and associated

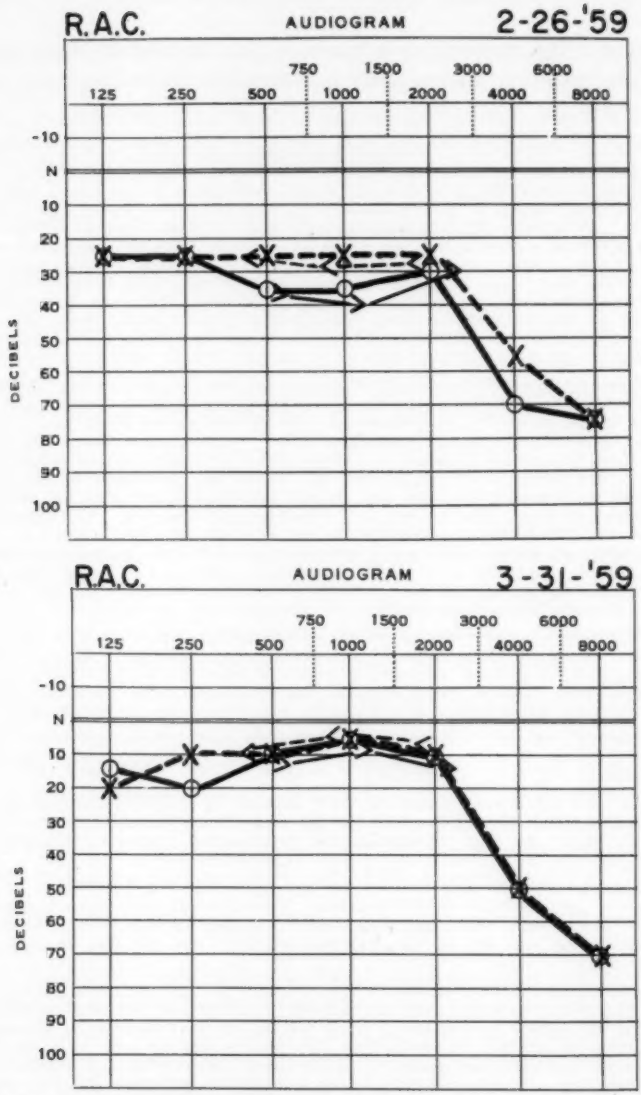

Fig. 1-a. Audiogram of patient with myxedema (Case 1) showing bilateral perceptive hearing loss.

Fig. 1-b. Audiogram of patient (Case 1) showing improvement after withdrawal of potassium thiocyanate.

perceptive hearing loss which has recovered following withdrawal of potassium thiocyanate.

Case 2. Mrs. J.L., a 65-year-old housewife was admitted to the University Hospital on August 2, 1959, with the chief complaint of general sluggishness and fatigue. Until 18 months ago she had always been in good health operating her own dry cleaning establishment, but then she began to slow down and feel tired. Four months prior to admission she had a heart attack and was hospitalized for six weeks. Three months prior to admission she had a cholecystectomy for cholelithiasis and following this operation she never quite regained her strength. At this time she could not stay up for longer than 30 minutes before lying down. Concomitantly, she has also noticed intolerance to cold, a very puffy face, dry skin and decreased hearing.

Examination showed an obese lady with fine, scaly, dry skin that is typical of myxedema. Her blood pressure was 110/70, pulse 64 and respirations 10. Examination of her eyes showed that they were nearly closed because of the puffy eyelids.

The laboratory findings on admission revealed normal blood and urine. The total cholesterol was 456 mg. per cent. The BMR was minus 24 per cent, the 24 hour iodine 131 uptake was 1.5 per cent and scintiscan of the thyroid showed complete absence of concentration of iodine 131. The PBI was 1.9 gamma per cent. Because of her hearing loss she was referred to the ear, nose, and throat clinic where examination of the ears, nose and throat revealed them to be essentially normal. The thyroid gland was not enlarged. Audiograms as shown in Fig. 2-a showed a bilateral, perceptive type of hearing loss, greater for the high than for the low tones. She had a bilateral discrimination loss of 32 per cent at 90 decibels.

The patient was placed on 8 mgs. of thyroid extract daily which was increased to 16 mgs. daily within one week. She began to feel better, have more energy, and was discharged on August 30, 1959.

After several weeks, while at home, it was noted by her daughter that the patient became more ambitious and was able to stay up for longer periods of time. In addition, she also noticed a gain in her hearing, and on November 25, 1959, audiograms were again taken (see Fig. 2-b). A noticeable improvement in hearing was recorded. Again the bilateral perceptive type of hearing loss prevails, the higher tones being involved more than the lower tones, but the degree of depression is not so great as that during hospital stay.

At the present time the patient is on 1½ gr. of thyroid per day, her weight is about 16 pounds less than at the time of her discharge in August, 1959, her pulse is 80 and her blood pressure 140/100. Because of her cardiac condition the amount of thyroid given her is being increased very slowly to prevent any precipitation of cardiac damage.

The deafness in the two cases reported above is unquestionably of the perceptive type, and more than likely the changes have occurred in the inner ear. Whatever these changes are they are certainly not so drastic as to be permanent. In order to determine histologically what these changes might be, a series of experiments on hypothyroid chick embryos was carried out. The hypothyroidism was produced by chemical

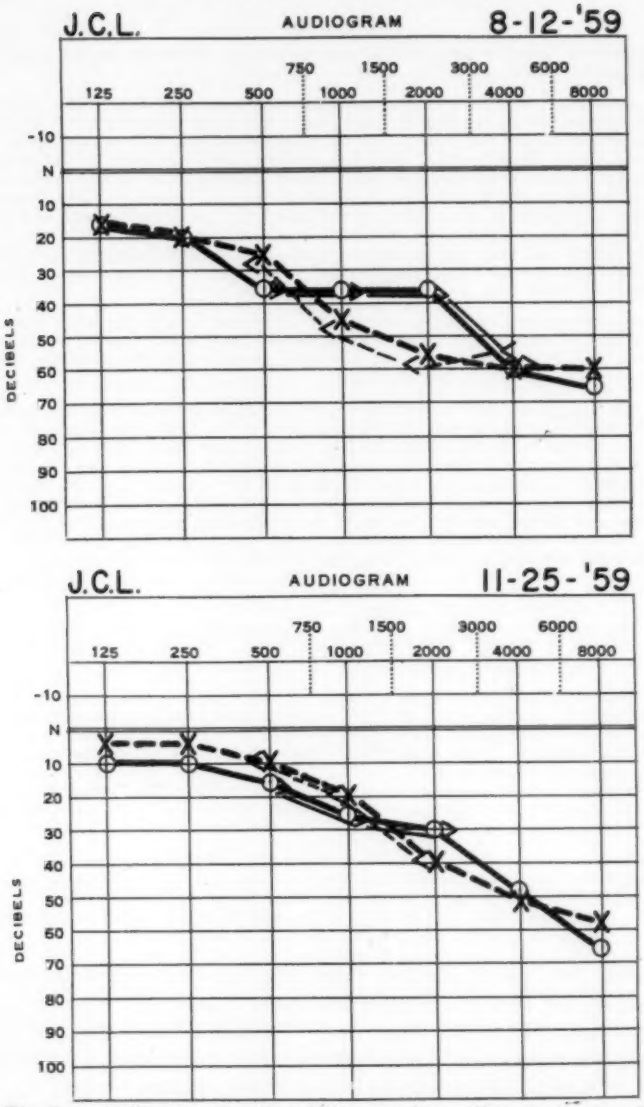

Fig. 2-a. Audiogram of patient with myxedema (Case 2) showing bilateral perceptive hearing loss.

Fig. 2-b. Audiogram of patient (Case 2) after treatment with dessicated thyroid.

means, and the temporal bones of the chicks were examined at the normal time of hatching.

PROCEDURE.

A total of 123 supposedly fertile eggs was placed in an incubator which was maintained at 37.5° C. and 70 per cent humidity. At various intervals the eggs were turned from their last resting position. Because of incubator mishaps, non-fertility, or early death of the embryo, only 89 eggs survived to be used experimentally. Of these, 17 were kept as normal controls, most of them hatching on the twenty-first day of incubation. Of those hatching four were sacrificed for histological study of the normal temporal bone.

The remaining 72 eggs were divided into three groups, depending upon the age at which injection with thiourea or plain chicken ringers was to be injected. The times selected were fourth, ninth and fourteenth days of incubation.

It has been shown[11] that 2 mg. of thiourea injected into a developing chick embryo has a destructive effect upon the function of the thyroid gland and produces a marked degree of hypothyroidism. For our purposes thiourea was dissolved in sterile chicken ringers[12] (2 mg. per ½ cc.) and refrigerated until used. Before this solution, or the plain ringers, was injected each was heated to 37.5° C. Injections were made under sterile conditions into the albumin in the narrow end of the egg after it had been cleaned with Lugol's solution. The injection sites were then sealed with liquid paraffin.

In the first group 20 eggs were injected on the fourth day of incubation. Seventeen were injected with ½ cc. thiourea in chicken ringers and three with ½ cc. plain chicken ringers. Of the 17 thiourea injected eggs, eight embryos died during incubation, one was sacrificed on the fourteenth day and eight on the twenty-first day. Of the three ringers injected eggs two died during incubation and one was sacrificed on the twenty-first day.

In the second group 49 eggs were injected on the ninth day of incubation, 43 were injected with ½ cc. thiourea in chicken

ringers and six with ½ cc. plain chicken ringers. Of the 43 thiourea injected eggs, 20 embryos died during incubation, two were sacrificed on the fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth and twentieth days of incubation and six on the twenty-first day. Hatching is invariably delayed in the thiourea injected chicks so a delayed-hatching embryo was sacrificed on the twenty-second, twenty-third and twenty-fourth day. Of the six ringers injected eggs four died during subsequent incubation, and two were sacrificed at the end of 21 days of incubation.

In the third group three were injected on the fourteenth day of incubation. All three were injected with thiourea in chicken ringers. Of these, two died and one was sacrificed on the twenty-second day.

Upon sacrificing, each embryo was fixed in Bouin's solution, decalcified, and eventually imbedded in paraffin for sectioning. The sections were cut at seven micra, mounted serially, stained with hematoxylin and eosin, and examined microscopically.

RESULTS.

Because the ears of the embryos injected on the ninth day of incubation failed to show any abnormality, the eggs injected with 2 mg. of thiourea on the fourteenth day of incubation were not studied further. All the embryos of eggs injected with chicken ringers, regardless of date of injection, failed to show any abnormality.

General changes were noted in the chick embryos injected with thiourea at four days' incubation. These chicks were all delayed in hatching and if hatching occurred they were underdeveloped. The yolk sac in each chick was large, and incompletely absorbed.

Fig. 3-a is a photomicrograph from a normal 21-day-old chick embryo showing a section of the root of the neck. The picture showing the root of the neck in Fig. 3-b is that of a 21-day-old chick embryo injected on the fourth day of incubation with 2 mg. of thiourea in ½ cc. chicken ringers. By

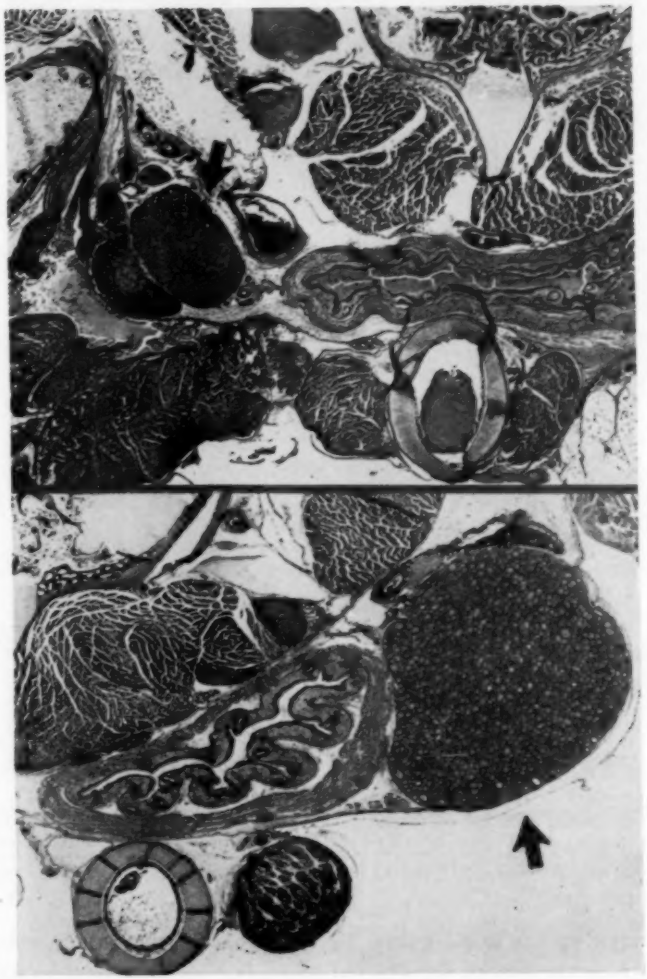

Fig. 3-a. Cross section of neck of 21-day chick embryo showing normal structures. Normal thyroid gland is indicated by arrow. (Mag. 50X.)

Fig. 3-b. Cross section of the neck of a 21-day chick embryo, injected with thiourea on the fourth day of incubation. The thyroid gland (arrow) is enlarged and the follicles contain more colloid than the normal chick embryo. (Mag. 50X.)

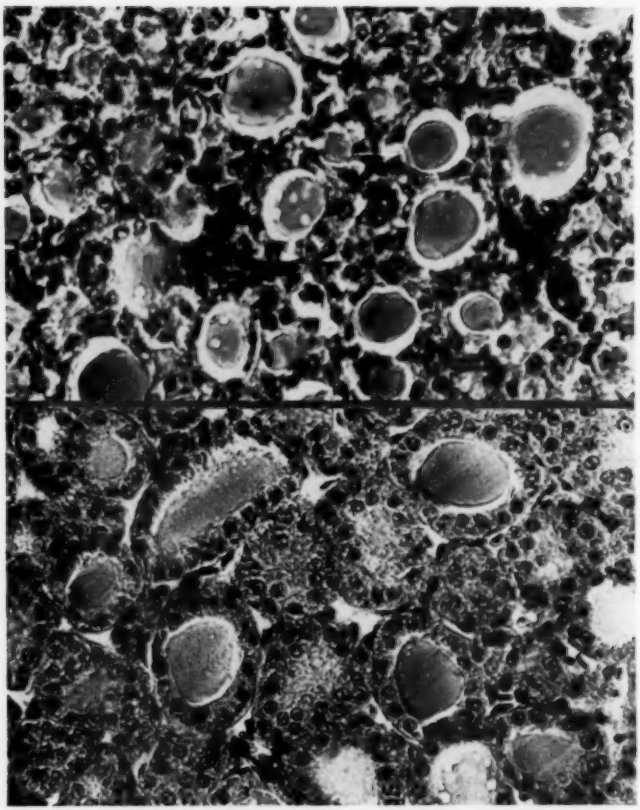

Fig. 4-a. The thyroid gland of the normal 21-day chick of Fig. 3-a. (Mag. 100X.)

Fig. 4-b. The thyroid gland of the chick of Fig. 3-b. The follicles are larger than normal, their lining is of a high cuboidal type and the amount of stored colloid is increased in amount compared to the normal. (Mag. 100X.)

comparing the two figures, 3-a and 3-b, it is possible to note the hypertrophy of the thyroid gland in the thiourea injected chick. The cervical muscles are hypertrophied and the cornification of the esophagus is low. These changes would be compatible with the findings of myxedema in which a goiter is present and the tissues edematous. Figs. 4-a and 4-b are

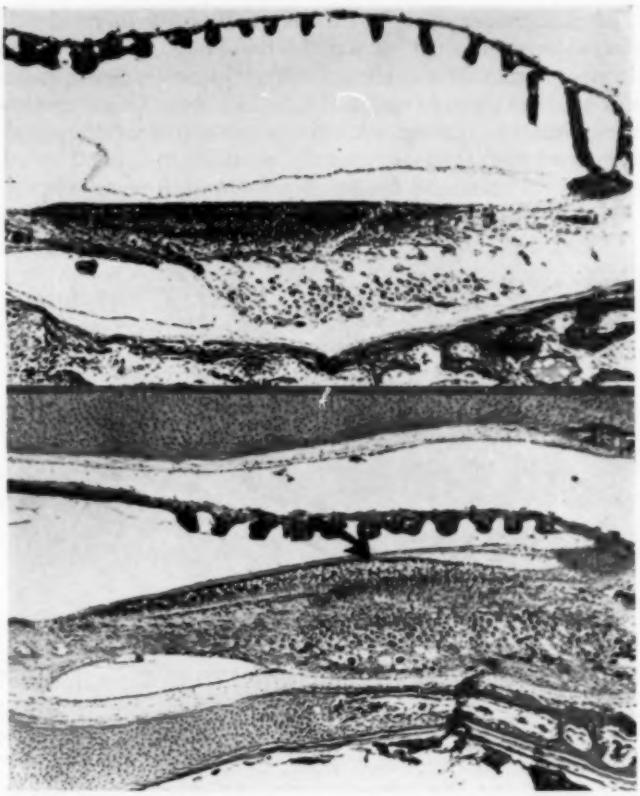

Fig. 5-a. The papilla of a normal 21-day-old chick embryo. The normal tegmen vasculosum, tectorial membrane, hair cells, and ganglion cells are shown. (Mag. 50X.)

Fig. 5-b. The papilla of a 21-day-old chick embryo injected with thiourea on fourth day of incubation. The tegmen vasculosum is present, and the tectorial membrane overlies the hair cells. Apparent is the single distinct row of hair cells separated from the supporting tissue by a clear layer of edema (arrow) which extends below the sensory epithelium for its entire length. (Mag. 50X.)

high magnification photomicrographs of the chick thyroid glands seen in Figs. 3-a and 3-b. The gland is normal in Fig. 4-a, but Fig. 4-b shows stored colloid in many follicles, hypertrophy of the follicular lining with a high cuboidal epithelium.

The changes noted in the ears of the thiourea injected chick embryos were limited chiefly to the inner ear. The only evidence of middle ear abnormality was some delay in conversion of the stapes from cartilage to bone. The stapes was present but not malformed. No hypertrophy of the middle ear mucous membrane, or closure of either the round or oval windows was seen. No fluid was present in these middle ears.

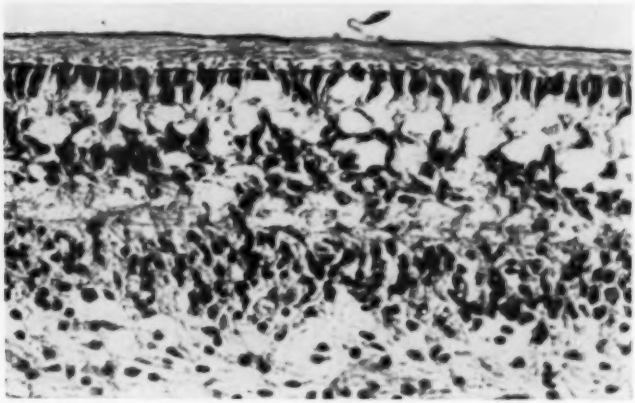

Fig. 6. The papilla of a 21-day-old chick embryo, injected on fourth day with thiourea. The hair cells are canine shaped, and the protoplasm is increased in amount and watery in appearance. The distinct layer of edema is just below the hair cells and separates the hair cells from the supporting tissues. (Mag. 200X.)

Fig. 5-a shows the normal organ of Corti of a 21-day-old chick embryo. One notes here the artifact of the tectorial membrane separated from the hair cells, but the hair cells are normal, with ovoid shape; likewise are the supporting tissues, ganglion cells and auditory nerve all normal.

Fig. 5-b shows the inner ear of a 21-day-old chick embryo injected on the fourth day of incubation with 2 mg. of thiourea in ½ cc. chicken ringers. Here the tectorial membrane is in contact with the hair cells, but the hair cells are separated from the supporting tissues by a clear layer of edema, several cell thicknesses in width. This edema has separated the hair cells from the supporting cells completely in some areas.

Fig. 6 is a high magnification photomicrograph of the organ of Corti of the chick shown in Fig. 5-b. This shows again the edematous area separating the hair cells from the supporting tissues; also the supporting tissues appear thinned and stretched out. The hair cells themselves have changed from a normal ovoid shape with scant protoplasm, to a columnar, tooth-like shape with increased amount of watery protoplasm. This layer of edema and the tooth-like hair cells were present in each chick that was injected with 2 mg. of thiourea at the fourth day of incubation. They were not present in any chicks injected after nine days of incubation or in any control or normal chicks.

DISCUSSION.

The two clinical cases have shown a direct relationship between hypothyroidism and deafness. They have also shown that this hearing loss can be reversed upon either the administration of the proper amount of thyroid or removal of the agent which inhibits thyroid activity.

The chick experiments demonstrate a direct relationship between edema in the developed sensory papilla and injection into the egg at a very early stage of development of the antithyroid compound, thiourea. The evidence is indirect but fairly conclusive that this change in the sensory area is the result of inhibited thyroid activity and not of the direct influence of thiourea. As Romanoff and Laufer[11] have pointed out the effect of the thiourea depends upon the stage of development of the thyroid gland at the time of injection. In our experiments injection of the antithyroid compound had no effect upon the auditory organ unless injected at least earlier than nine days of incubation, and the changes that were produced were always accompanied by hypertrophy of the thyroid gland.

The chick organ of Corti differs considerably from that of the human. There are no Deiters' cells nor rods of Corti. The cochlea consists of only one-half turn with the sensory cells supported by columnar cells. The chick auditory sensory area is more logically called the acoustic papilla. It may be un-

warranted to assume that because hypothyroidism in the developmental stages of the chick results in edema of the sensory area by the time of hatching, something similar could occur in the human; yet it is not inconceivable, and the reversibility of the effect in the human supports its plausibility. Perhaps occasional changes in the inner ear occur with slight abnormality of thyroid activity, and it is possible that these might, therefore, be reversible with treatment of the thyroid abnormality.

SUMMARY.

Two cases of hypothyroidism with associated perceptive deafness have been described. Treatment with thyroid in one instance and cessation of the administration of a drug inhibiting thyroid activity in another reversed this hearing loss.

Experiments conducted by injecting thiourea into fertile chick eggs at a very early stage of development showed, at the age of hatching (21 days of incubation), marked hypertrophy of the thyroid gland and edema in the area of the sensory supporting cells of the acoustic papilla.

The possible relationship between the occurrence of this edema and the reversibility of the hearing loss is discussed.

ACKNOWLEDGEMENT.

We are indebted to Miss Maxine Clapper for her tireless care of the incubating eggs and for her skillful preparation of the overwhelming amount of histological material.

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THERAPY OF SUDDEN LABYRINTHINE DEAFNESS.*

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As the name implies, sudden deafness can and does strike like a bolt from the blue and, like it, is almost always associated with a roaring tinnitus. It may or may not be associated with dizziness.

The etiology of sudden deafness of labyrinthine origin is still obscure. Information about it is next to impossible to obtain because the deafness is very seldom associated with events that kill the patient.

REVIEW OF LITERATURE.

Treatment for sudden deafness has varied greatly all over the world, depending mainly upon the attending otologist's opinion as to the etiologic factors at play. Certain circumstances associated with the onset may indicate or at least lead one to suspect the cause in some cases. Before 1950, very little had been written on sudden deafness and its treatment. Surgical treatment such as the fenestration operation has been confined mostly to Europe.

Opheim[1] in 1950 expressed the view that sudden deafness is caused by an acute rise of pressure in the labyrinth. This rise, he said, opens a road to rational intervention against this condition, which otherwise has such an unfavorable prognosis. He performed fenestration operations on three of his patients for their decompression effect. At operation he attempted to leave the ossicular chain intact. In all these patients the hearing improved somewhat, but not to a serviceable level. On puncture of the labyrinth the fluid was found

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*Read at the meeting of the Middle Section of the American Laryngological, Rhinological and Otological Society, Inc., Chicago, Ill., Jan. 18, 1960.

†Section of Otolaryngology and Rhinology, Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

Editor's Note: This manuscript received in The Laryngoscope Office and accepted for publication Feb. 8, 1960.

to be under pressure in one patient, but not in the other two. Opheim stipulated the following conditions for operation:

1. The loss of hearing must be complete to the extent that such a condition is recognizable, the function of the other ear being normal.

2. The patient must be available for treatment early enough in the course of the disease that it may be supposed that damage to the neurosensory mechanism has not become irreparable.

Beichert,[2] working with Zöllner, offered a rather unique classification made up of two groups:

Group 1 consisted of patients whose deafness could be attributed to psychoemotional factors that work through the vegetoneural system upon the neurosensory mechanism. His five patients in this group had dizziness associated with the deafness. One of these patients underwent a fenestration operation by Zöllner.

This patient, a 38-year-old woman, experienced sudden total loss of hearing in the right ear associated with severe dizziness. Zöllner used a postauricular incision, leaving the ossicles intact. The inner ear was filled with blood. As one would expect, the deafness which was total before operation remained so.

The other patients in this group were treated as though they had Ménière's disease.

Group 2 consisted of patients whose deafness was thought to be caused by a mechanical effect on the cervical sympathetic nervous system or on the nerves surrounding the vertebral artery by osteochondrosis of the cervical part of the spinal column. Sudden deafness and roaring tinnitus were the only symptoms. None of the patients had dizziness. It seemed that all developed their symptoms while at work, and X-ray examinations of the cervical spine showed arthritic changes. One patient, a 39-year-old man, is reported on in detail:

Sudden loss of hearing with tinnitus occurred one morning. The patient had picked cherries all day the day before. The results of a complete general examination were negative except for arthritic changes of the cervical spine on X-ray examination. An audiogram, however, showed marked deafness on the left (between 50 and 70 decibels). Treat-

ment with rest in bed and stretching of the neck was started on the seventh day. Five days later, hearing had returned to normal except for moderate loss in the high frequencies.

To me this approach seems a little farfetched, since many patients with arthritic changes in their cervical spine have no history of sudden deafness.

Svane-Knudsen,[3] of Denmark, performed a fenestration operation on one of his patients six days after the onset of deafness. What could be seen of the labyrinth looked normal. Hearing did not return.

In the United States, many of the publications on this subject indicate that the patients were treated as though they had Ménière's disease, in the hope that irreversible changes had not already taken place in the cochlea.

A different approach to therapy might possibly come from investigations by Bocca and Giordano[4] in 1956. They reported 28 cases in which the deafness occurred after recent exposure to a draft or cold or in the course of an infection such as influenza or the common cold. They presumed that the process must be very similar to that causing Bell's palsy.

Van Dishoeck and Bierman[5] studied 100 cases of sudden deafness. In 40 of these they found evidence that a virus infection was the cause of the sudden perceptive deafness. They specifically blamed the mumps virus, but admitted, however, that vascular disorders may be common. They had no specific treatment to offer.

Recently Saunders and Lippy[6] examined nine patients who had sudden severe deafness. Four of these definitely, and two probably, had mumps. Mumps and influenza antibodies were determined on blood specimens from these nine patients, from 10 additional patients with Bell's palsy, and from 370 unselected patients (the control group). They concluded that subclinical mumps is a common cause of sudden deafness and Bell's palsy.

It certainly seems possible that sudden deafness might be of virus origin in many of the patients in the younger age

group; but even then, as has been stated by Fowler,[7] the hearing loss might be basically vascular in origin.

I still feel that in most patients, at least in the middle and older age groups, the hearing loss is of vascular origin. It seems that there are at least two objections to the mumps virus theory: *1.* Clinical mumps seldom recurs. *2.* Mumps is such a widespread disease that few individuals escape it during childhood.

If mumps were suspected, I would still try the effect of vasodilation, although if the patient were seen right after the onset of deafness, I might also give mumps vaccine. The recommended dosage for children as well as for adults is two injections of 1.0 cc. each. The interval for optimal immunization is not known, but one week between injections is suggested.

The results of treatment of sudden deafness have, all in all, been disappointing; the main reason, I hope, is that most patients come late for treatment. The obvious reason, of course, is that the exact cause is not known in each case. Fowler[7] mentioned five patients with severe sudden hearing loss of the neurosensory type who had spontaneous and gratifying recoveries. This certainly was unexpected and, as Fowler states, it makes the rationale of hospitalization for intravenous injections of procaine and for heroic anticoagulation therapy, or any treatment for that matter, difficult to defend.

Fowler treated 30 patients who had hearing loss of three weeks' duration or less. Fifteen patients received both nicotinic acid, 50 to 100 mg. three times a day, and injections of 250 cc. of 0.1 per cent solution of procaine hydrochloride; three of these manifested gratifying improvement. Five received nicotinic acid alone; one was much improved. Ten received anticoagulant drugs in addition to nicotinic acid and procaine, but most of them received the anticoagulation therapy so late that it could hardly be expected to have much effect on the small blood vessels that must be involved in labyrinthine apoplexy. In two patients in whom the treatment was started early, the result was very encouraging.

Fowler gives the patient heparin for immediate effect. He injects 50 to 75 mg. deep into the subcutaneous tissue every six hours for five or six days. He then administers dicumarol or warfarin (coumadin), which can be taken in tablet form. Prothrombin time has to be checked regularly. If this type of treatment is used, I suggest close supervision and guidance by the internist.

Several investigators say that practically every patient having arteriosclerosis obliterans and acute vasospastic disease presents some degree of sludging and intravascular abnormality, as seen in the bulbar conjunctival vessels. Most patients also appear to have a clinically significant element of vasospasm.

PATIENTS STUDIED AT THE MAYO CLINIC.

Previously, I reported on a study of 178 patients with sudden deafness.[8] Patients whose deafness was from more or less obvious causes, such as from injuries and local infections, were not included. All patients with sudden deafness, so far as my colleagues and I have seen them, have a perceptive deafness, mostly of end-organ type, with different degrees of recruitment. The deafness may vary greatly from a total loss of hearing to a slight dip involving only one or two frequencies.

The following illustrations present possible etiologic factors at play. As you see, most of them come under the classification "vascular accident" (89 patients) or "Ménière's disease" (56 patients). I use the term "vascular accident" because it implies vascular damage but does not specify type. The majority of the 178 patients studied were spread over the older age groups, corresponding to those in which coronary occlusion is common. Parker and associates[9] estimated that 85 per cent of 3400 patients with angina were in the age group 40 to 69 years. Of the 89 patients with deafness due to vascular accident in my series, 64.1 per cent were in this age group; however, there was one significant discrepancy: 3.6 per cent of patients with angina were in the age group 20

to 39, whereas 30.3 per cent of the 89 with deafness were in this age range.

This is difficult to explain, as the blood supply to the labyrinth is such that even minor vascular changes might cause early symptoms. I was able to recheck 20 of the 27 patients (30.3 per cent) in the age group 20 to 39 years. Three of these subsequently had vascular accidents elsewhere in the body. This may or may not be significant; however, I began to suspect that early atherosclerotic changes may be responsible for the sudden deafness, at least in some patients. Four patients with sudden deafness were checked more thoroughly, including determination of cholesterol, fatty acids and total lipids. Below are reports on two of these patients.

Case 1. A 40-year-old mechanic developed sudden vertigo while firing his furnace in 1952. It was a rather severe, spinning vertigo with nausea and vomiting. Ten days later, he had sudden deafness in the right ear and also severe dizzy spells. Then he was well until 1958, when he came to the Mayo Clinic because of pain across his chest. The ears looked normal, with normal hearing on the left and total deafness on the right. The corneal reflexes were intact, and he had no nystagmus. The caloric test revealed a hypoactive right equilibratory labyrinth.

The results of general examination were not remarkable. The cardiac findings, including the electrocardiographic picture, were normal. The blood pressure was 110 mm. of mercury systolic and 70 diastolic. The ocular fundi showed minimal narrowing and sclerosis of the arterioles. Blood cholesterol measured 305 mg. per 100 cc. on two occasions (normal 150 to 250 mg.), fatty acids 398 and 444 mg. (normal 350 to 400), and total lipids 703 and 749 mg. (normal 400 to 659). Because of these findings, the internist thought the patient had atherosclerotic disease.

Case 2. A physician, aged 46, had sudden blurring of hearing on the left, with roaring tinnitus, on February 15, 1957. The ear felt as though it had fluid in it. He had a strong family history of coronary disease. On examination the following day, the ears including the drum membranes looked normal. The audiogram showed a sharp island loss of hearing at 2000 cps. The results of general examination were negative except for rather high levels of blood fats. Cholesterol measured 190, fatty acids 405, and total lipids 595. He was immediately started on treatment with a low fat diet and 200 mg. of nicotinic acid given 20 minutes before meals and at bedtime. The hearing returned to normal in two weeks. When I talked to him recently, his hearing seemed still to be normal. I might add that he has decided to stay permanently on a low fat diet.

RESULTS OF TREATMENT.

With the sludging and vasospasm in mind, my colleagues and I concentrated more on using one of the vasodilators, and for several years nicotinic acid has been the drug of choice.

At first we started with nicotinic acid tablets, 100 mg. before breakfast and 100 mg. before supper, on an empty stomach. If primarily we have suspected that the level of blood fats might be high, we have tended to increase the dosage substantially. According to Achor and Berge,[10] and later Parsons and Flinn,[11] blood cholesterol has been decreased a significant degree by using 1 gm. of nicotinic acid three times daily with or after meals. This is five times the usual dose. Patients should also go on a low fat diet and stay on it for the rest of their lives.

Other methods, now more or less investigative, are at hand, which make it possible to lower the concentration of blood cholesterol in man. Favorable responses in the blood lipid pattern can be effected by a diet low in fat, by the addition of unsaturated vegetable oils to the diet, and by the administration of such agents as plant sterols, estrogens and heparin. These regimens have been reported as improving the survival rate for persons who previously had had coronary occlusion.

So far, the results of treatment have been very disappointing, to say the least, and one of the main reasons could be that patients come so late for treatment. In such a fine mechanism as that of the end organ of hearing, irreversible changes may take place quickly.

If the hearing loss has lasted more than three weeks and the hearing does not fluctuate, one must conclude that the damage to the cochlea is permanent and that treatment directed toward improving the hearing is useless.

In checking over the records of these patients, it was surprising and disconcerting to see how many of them were treated for a long time with inflation of the Eustachian tube.

SUMMARY.

Since nothing definite is known about the etiology of sudden deafness, the results of treatment are difficult to evaluate. I believe, however, that the cause in most instances is to be considered a vascular accident and that treatment should consist of large doses of nicotinic acid and a diet low in

saturated fats. Treatment should be directed toward the patient as a whole, since the vascular accident in the ear might be a forerunner of pathologic changes in more vital parts elsewhere in the body.

In conclusion, may I say that we are still playing with the problem, like a cat with a mouse, but so far we "cats" have not yet had the pleasure of swallowing the morsel.

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PHASE-CONTRAST PHOTOGRAPHY OF THE DIFFERENTIATED LIVING CELLS OF THE INNER EAR.

TAWFIK GIRGIS, M.D.,
(By Invitation),
Chicago, Ill.

(This was a Movie Presentation.)

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AUDIOLOGICAL MANIFESTATIONS OF LESIONS IN THE AUDITORY NERVOUS SYSTEM.*

JAMES JERGER, Ph.D.,
(By Invitation),
Evanston, Ill.

For the purpose of this discussion, it is useful to divide the auditory nervous system into four parts, as follows:

1. Cochlea.
2. VIIIth Nerve.
3. Brain Stem.
4. Auditory Cortex.

Experience gained over the past three years leads us to believe that lesions at each of these four sites are characterized by distinctly different patterns of response to a diversified battery of auditory tests. There seems to be a unique patterning of response corresponding to each of these four sites of lesion.

The basis for this patterning seems to be at least four-fold: first, the diseased cochlea produces a number of unusual symptoms not encountered in any other part of the system. It manifests, for example, loudness recruitment, non-linear distortion, and a rather astonishing capacity to appreciate small changes in sound intensity. It may be fruitful to consider all of these manifestations as symptoms of a basic *disorder in the "biological amplifier"* of the auditory system, as described by Davis.

Second, the diseased VIIIth nerve produces a quite unique phenomenon encountered nowhere else in the system, a rather marked inability to maintain response under sustained stimulation. During sustained stimulation by a pure tone, for

*Read at the meeting of the Middle Section, American Laryngological, Rhinological and Otological Society, Inc., Chicago, Ill., Jan. 18-19, 1960.
Editor's Note: This manuscript received in The Laryngoscope Office and accepted for publication Feb. 8, 1960.

example, the threshold intensity may rise 40-50 db in as little as 60 seconds. The effect is so dramatic that many of our colleagues fail to appreciate its reality until they have observed it personally. In a previous publication, we have referred to this as the phenomenon of *"abnormal auditory adaptation."* In some respects, however, the term *"relapse"* might be more appropriate.

In addition to these localized sets of symptoms, there appear to be two rather general principles. One of these states that *the subtlety of the auditory manifestation increases as the site of lesion progresses from peripheral to central.* An illustration of this principle is the audiogram itself. Thresholds for pure tones represent relatively simple judgments in any hierarchy of auditory tasks. In accordance with the "subtlety principle," therefore, they are most affected by lesions of the peripheral apparatus (*i.e.*, the middle ear and cochlea), less affected by VIIIth nerve lesion, and affected only slightly, if at all, by lesions within the central nervous system. Another way of viewing this principle is in terms of the subtlety of the auditory manifestations of lesions at progressively more central sites. At the peripheral level the presence of a lesion may be demonstrated with relatively simple tests, such as threshold for pure tones or response to isolated monosyllabic words. At more central sites, however, the presence of a lesion can often be demonstrated only by means of considerably more subtle auditory tasks.

The second general point concerns what we consider the *"bottleneck principle."* This states, in effect, that the process of transmitting the informational content of a complex auditory stimulus (*i.e.*, speech) encounters a very real bottleneck in the VIIIth nerve and lower brain stem. Lesions at these sites limit the ability to understand speech drastically. One may observe, for example, cases of VIIIth nerve tumor with a very poor speech discrimination score in the face of only slight reduction in the audiogram. Brain stem lesions may produce severe discrimination problems with no depression in the audiogram whatsoever.

Lesions either more peripheral or more central than the

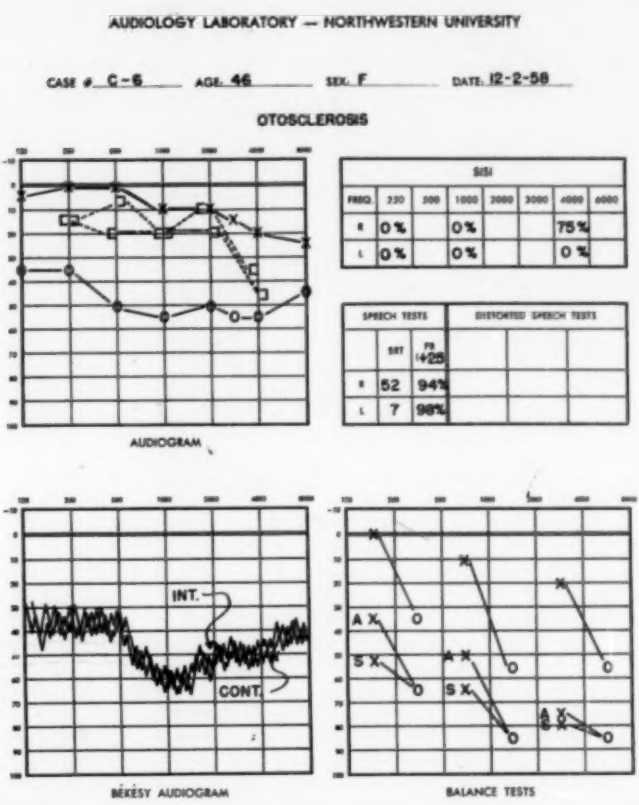


Fig. 1.

VIIIth nerve-brain stem region apparently have much less effect on the successful transmission of complex stimuli. A possible exception to this generalization exists in the case of Ménière's disease during its active phase when speech discrimination may be severely involved.

In general, however, neither cochlear nor cortical lesions seriously impair the ordinary speech discrimination score.

The following five cases illustrate these principles more

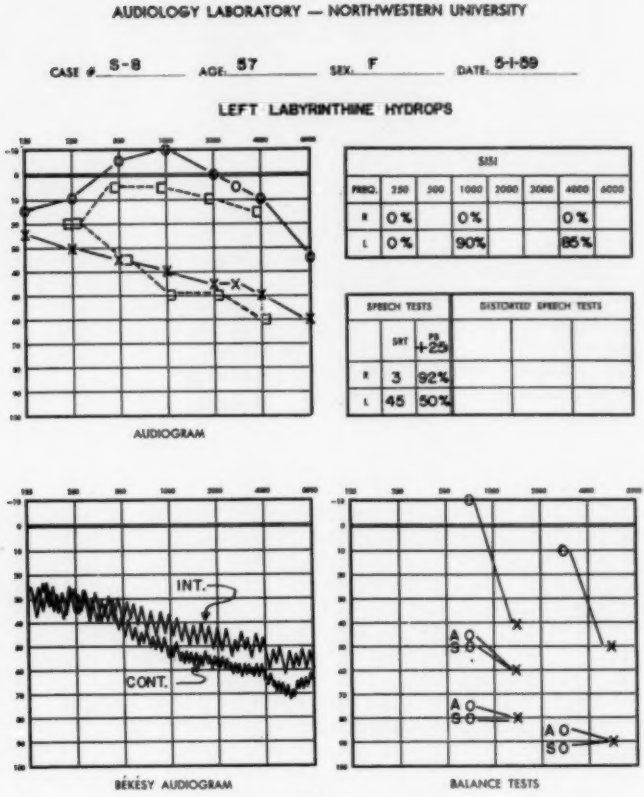


Fig. 2.

concretely. They represent, respectively, unilateral lesions in the middle ear, cochlea, VIIIth nerve, brain stem, and temporal cortex.

Fig. 1 shows auditory test results in a case of left otosclerosis. Note the low SISI scores, absence of loudness recruitment, and normal Bekesy audiograms, as well as the excellent speech discrimination score. The only audiological manifestation of a hearing loss is the loss in threshold sen-

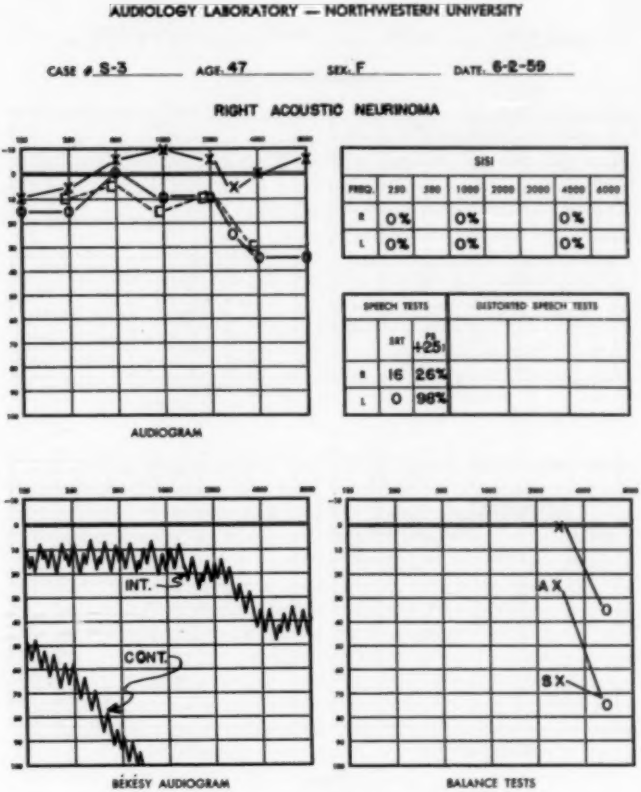


Fig. 3.

sitivity on the affected ear. On all of the other auditory tests this ear behaves exactly like a normal ear.

Fig. 2 shows test results in a case of unilateral Ménière's disease. Now we see all the signs of a diseased cochlea; high SISI scores, loudness recruitment, and the Category II Bekesy audiogram, so characteristic of inner ear lesion. The speech discrimination score is reduced, but not too much in view

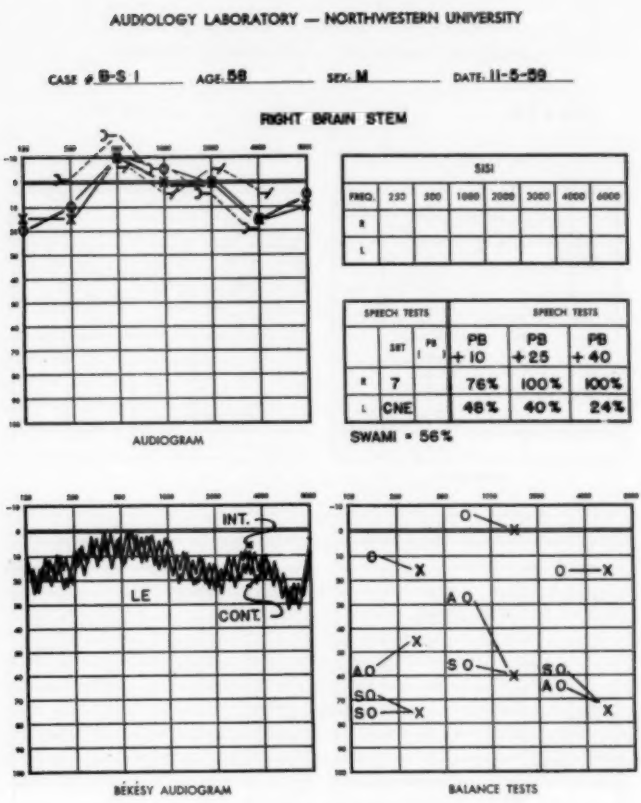


Fig. 4.

of the unforunate state of the sensory receptor mechanism. In any event these three signs, high SISI score, loudness recruitment, and Category II Bekesy audiogram are unique to lesions affecting the cochlea.

Fig. 3 shows a quite different picture in the case of acoustic neurinoma. Here the SISI score is low, loudness recruitment is absent, and the Bekesy audiogram is Category III, exemplifying the rather marked adaptation or relapse under sustained stimulation, a symptom apparently quite unique to

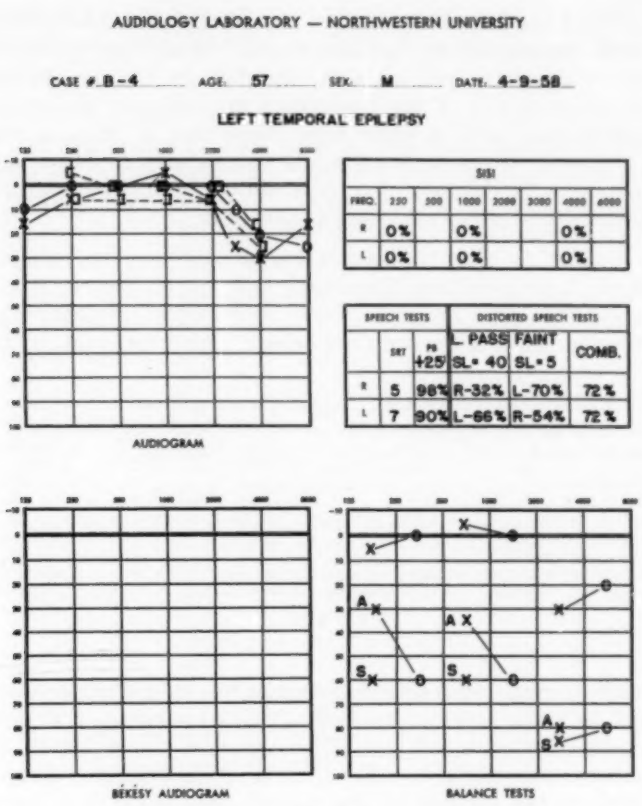


Fig. 5.

lesions of the VIIIth nerve. Notice, also, the astonishingly low speech discrimination score despite only a mild loss in pure-tone threshold sensitivity.

Now we are in the bottleneck region, and one is led to suspect that the loss of a substantial number of VIIIth nerve fibers has a much more profound effect on the capacity to transmit speech than on the capacity to transmit faint pure tones.

Fig. 4 shows test results in a case of right-sided brain stem lesion consequent on vascular insult. Pure tone thresholds are relatively normal on both ears, but, on the ear opposite the affected side of the brain stem, the ordinary speech discrimination score is quite low. Now this is really a very remarkable situation, a markedly reduced speech discrimination score in the face of a quite normal audiogram, and the defect shows up on the opposite side only.

Finally, in Fig. 5, we see a case of left temporal epilepsy. Here, both pure-tone thresholds and speech discrimination scores are quite normal. There is really no evidence of a "hearing loss" in the ordinary sense. The involvement of the

	Relative Subtlety of Auditory Task		
Site of Lesion	Pure-tone Acuity	PB Discrim.	Distorted Speech
Middle Ear	P	O	O
Inner Ear	P	S	—
VIIIth Nerve	S	P	—
Brain Stem	O	P	—
Temporal Cortex	O	O	P

O = Not affected. P = Primarily affected. S = Secondarily affected. — = Cannot be assessed.

Fig. 6.

auditory system can be demonstrated, but only if the auditory task is made sufficiently difficult. One method is to pass speech through a low-pass filter before delivering it to the patient's ear. This has the effect of attenuating the consonantal sounds relative to the vowels and makes the speech "muffled" and rather difficult to understand. In this auditory task the unilateral defect shows up quite clearly. The discrimination score is now considerably lower on the ear opposite the affected temporal lobe.

These cases illustrate what we believe to be the salient audiological manifestations of lesions in the auditory nervous system. At the risk of oversimplification, it seems to us that the entire picture is quite orderly.

Fig. 6 summarizes our present view. We believe that the auditory manifestations of lesions at various sites within the

auditory nervous system are rather meaningfully related to the subtlety of the auditory demands made by various kinds of tests.

Acuity for pure tones, for example, is maximally affected by peripheral lesions and progressively less affected as the site of lesion moves centrally. Ordinary speech discrimination is maximally affected in the bottleneck region of the VIIIth nerve and brain stem, less affected by cochlear lesion, and not at all by either middle ear or cortical lesion.

Finally, at the extreme central level only the ability to perform relatively subtle and difficult listening tasks is demonstrably affected.

The principles and generalizations presented here are based on very incomplete evidence. They should be interpreted as guideposts for further research rather than fully documented conclusions.

SECTION OF OPHTHALMOLOGY AND OTOLARYNGOLOGY OF SOUTHERN MEDICAL ASSOCIATION.

The Section of Ophthalmology and Otolaryngology of the Southern Medical Association announces that they are now accepting papers by physicians of either specialty living in the area of the Southern Medical Association for consideration for presentation at the next annual meeting to be held in St. Louis, Mo., from October 31 to November 3, 1960.

The paper or an abstract of the paper should be sent directly to the Secretary, Dr. Albert C. Esposito, Suite 1212, First Huntington National Bank Building, Huntington, W. Va., as soon as possible.

NEUROVASCULAR DYSFUNCTIONS OF THE EIGHTH NERVE.*†

SAM E. ROBERTS, M.D.,

Kansas City, Mo.

My presentation in the workshop today is entirely clinical. It is not statistical as there were no controls. It is a metabolic study in which *hypometabolism* will be stressed. Acoustic trauma, bacterial, viral and other etiologic factors have been excluded. Opinions and conclusions are hypothecated upon the investigations of 157 patients with adequate physical, serologic and other examinations.

Positive statements obviously cannot, and should not, be made until clinical and basic research are better correlated.

Historians of otology will probably record the years of 1950 to 1960 as the decade of greatest surgical achievement on the bony capsule of the labyrinth.

Cardiovascular history will, I am sure, also record that in this same period more has been done to crystalize our knowledge of cardiovascular diseases than in all the preceding centuries. We must recall that James B. Herrick of Chicago made cardiac history when he gave his first complete clinical description of coronary occlusion as recently as 1912. This was 254 years after Wepfer, a Swiss physician, demonstrated the fact that apoplexy is due to cerebral hemorrhage.

I believe the next ten years, 1960 to 1970, will show a significant advance in the understanding, prevention and treatment of neurovascular dysfunctions of the entire VIIIth nerve. We are now in the thinking stages only.

Such men as Fowler, Sr., Fowler, Jr., Hallberg, Kimura,

*Read at the meeting of the Middle Section of the American Laryngological, Rhinological and Otological Society, Inc., Chicago, Ill., Jan. 18, 1960.

†From the Department of Otolaryngology, University of Kansas Medical Center, Kansas City, Kans.

Editor's Note: This manuscript received in The Laryngoscope Office and accepted for publication Feb. 8, 1960.

Perlman and many others are doing superior jobs of creative and provocative thinking on this subject.

Fowler, Sr.,[1] for example, when discussing presbycusis states, "the basic causes in both the young and the aging are similar insofar as they are dependent upon a disordered metabolism, particularly a disordered oxygen supply." He further emphasizes, "even when there appears to be no general hypometabolism or hypothyroidism there may be local hypometabolism."

We have far too long attempted to visualize otologic pathology through a tiny speculum. When we are able to construct mentally an ear speculum the size of the human body, otology will advance even more rapidly.

Since there is no definitive laboratory proof of an organic lesion in hypometabolism, the clinical diagnosis depends entirely upon the awareness of the physician and a careful and thoughtful history. The history usually reveals a vague borderline state of ill health. Symptoms are often so bizarre and puzzling even to the erudite physician that these unfortunate patients will be told, "there is absolutely nothing physically wrong with you," leaving the distinct connotation that the condition is nervous or mental. This often starts the trek to our over-crowded institutions for nervous and mental illnesses.

Fatigue is a common symptom of these patients who suffer complete exhaustion by mid-day due to hypoglycemia. The fact that these persons frequently have had no breakfast, or an inadequate breakfast, renders them hypoglycemic before they start the day's activities!

Hypometabolism chiefly affects three classes of people: first, business men and women whose occupations are largely sedentary and primarily mental; second, persons with poor eating habits (this includes overindulgence in beverages and foods at the evening meal, when the body requires the least energy-producing foods. Such eating habits tend to produce an undesirable, and often a dangerous obesity, which may occur even in the very young); and, third, chain smokers

and those getting very little, if any, exercise—active or passive.

E. J. Fowler, Jr.,[2] states, "Blood sludge has been observed in many instances coincidentally with disorders of the ears and in this author's opinion it is frequently involved in the etiology of tinnitus, vertigo and deafness."

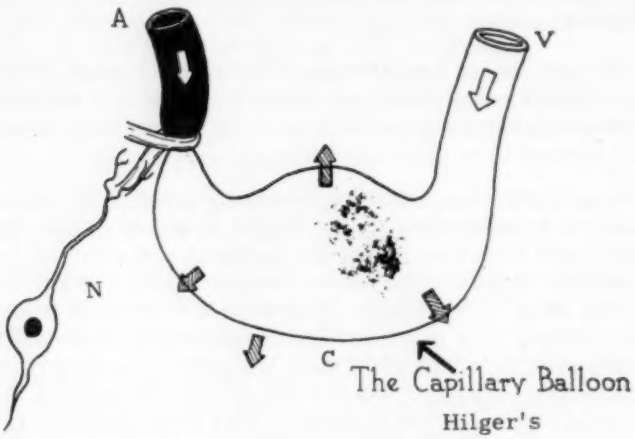


Fig. 1. Hilger's mechanism of arteriolar spasm. The transudation between endotheal cells results in extravascular fluid. The latter compresses lymph capillaries and localized statis causing sludged blood. A—artery; V—vein; C—capillary; N—nerve.

I am indebted to Jerome Hilger[3] for a graphic illustration of sludged blood (see Fig. 1).

Hallberg[4] points out, "The most common cause of sudden deafness is thought to be vascular accidents . . . . and that these lesions may consist of thrombosis, embolism, spasm, sludging or other conditions of/or in the vessels carrying blood to the labyrinth."

Kimura and Perlman[5] in their basic investigation of arterial obstruction of the labyrinth conclude, ". . . one hour after

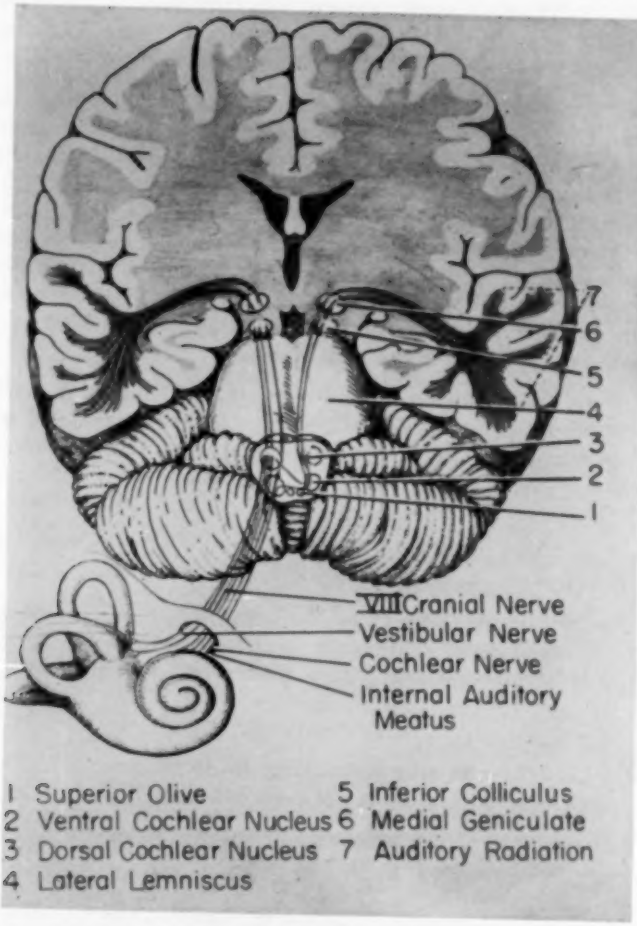


Fig. 2. VIIIth nerve pathways where neurovascular dysfunctions are likely to occur.

arterial obstruction . . . the entire cochlear nerve stained poorly . . ."; "Myelin droplets appeared in four days . . ."; "This experimental arterial occlusion produced a severe localized brain stem lesion."

My impression, clinically derived, is that vascular dysfunctions and their sequelae, such as anoxia, are the most common cause of all chronic dysfunctions of both divisions of the VIIIth nerve. These dysfunctions may occur in the labyrinth, in the central pathways, in the associated nuclei or in the control areas in the brain stem extending to the cerebral cortical terminations (see Fig. 2). Another impression, also clinically derived, is that progressive VIIIth nerve degeneration could be nicely explained on the basis of slow deterioration of myelin sheath of the VIIIth nerve and, later, axon destruction.

Dennis and Calkins[6] reported a case of total blindness with bilateral optic nerve demyelination (Devic's disease). It seems reasonable by comparison that the VIIIth, another cranial nerve, could be affected in the same manner* (see Fig. 3).

What affects the myelin sheath in one part of the body most likely affects it elsewhere.

The preganglionic fibers of the autonomic nervous system are also myelinated. This could be at least one cause of autonomic imbalances, which control the entire vascular system.

HISTOANATOMY.

Shambaugh[7] was among the first to demonstrate the distribution of blood vessels in the labyrinth (see Fig. 4).

Williams[8] has shown a schema of the histoanatomy of the uncoiled cochlea (see Fig. 5).

HISTOPATHOLOGY.

Vascular histopathology is essentially the same in all parts of the body. It matters not whether the pathology is in the

*This affords an admirable opportunity for a joint comprehensive clinical research program. The occulist can visualize the neurovascular changes in the fundus; the otologist is able to measure the destructive changes in the acoustic nerve.

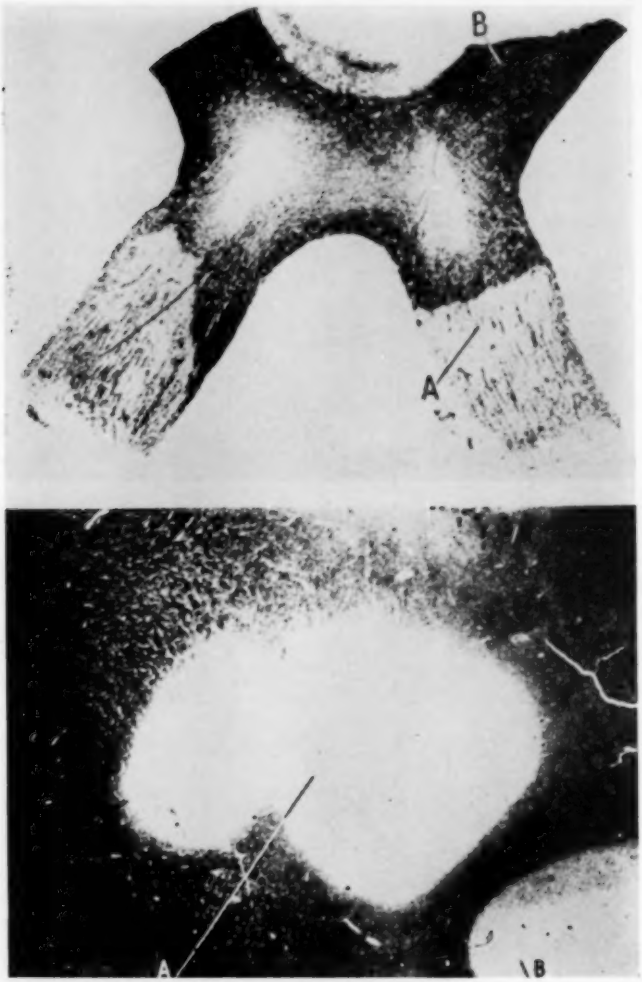


Fig. 3. Optic chiasm showing demyelination of optic nerves (A). The optic tracts are not involved (B X 8). (Dennis and Calkins.)

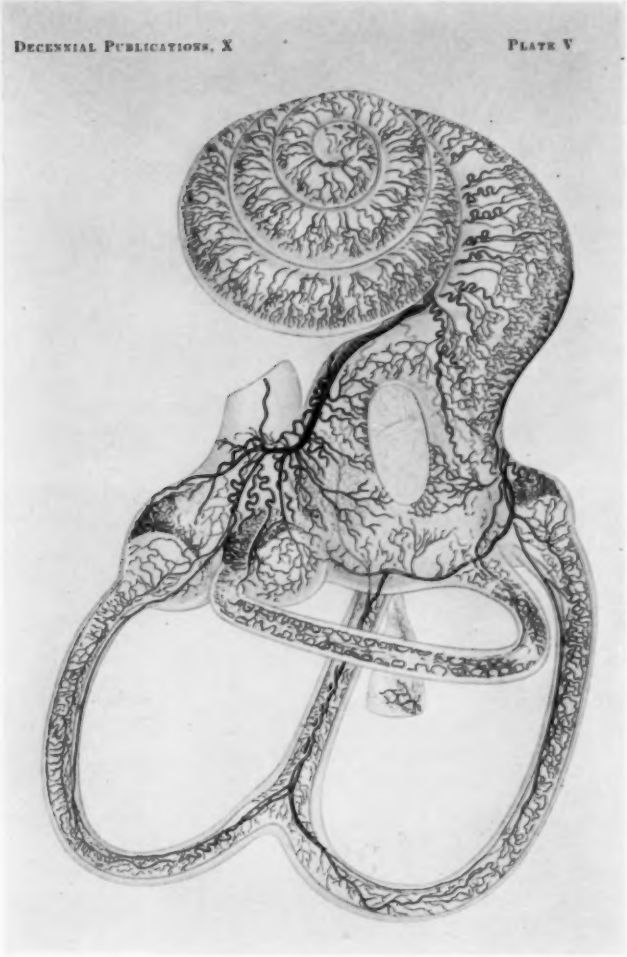
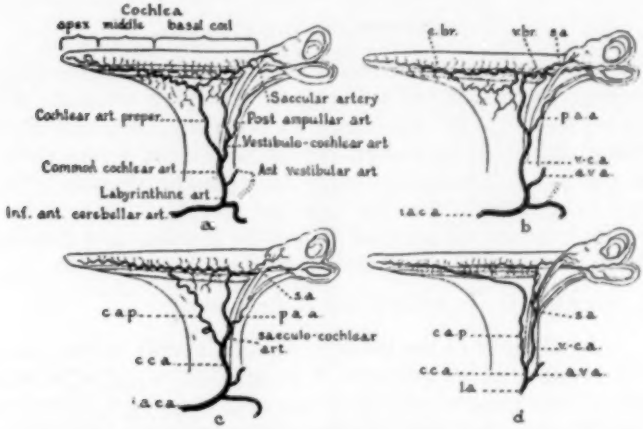


Fig. 4. Labyrinthine Circulation. (Geo. S. Shambaugh, Sr.)

tiny vessels of the labyrinth, not as large as a human hair, or in the larger cerebral or conorary arteries.

Since neuro-histopathology of the VIIIth nerve after it leaves the labyrinth is almost nonexistent, demyelination (diffuse or patchy seems a reasonable postulation.*



Distribution of blood supply: *a*, *b*, and *c*, according to Nabeya; *d*, Siebenman's schema. The branches of the anterior vestibular artery are not shown.

Fig. 5. Blood supply of the labyrinth. (From Henry Williams' "Meniere's Disease," Chas. C. Thomas, 1952.)

Whenever neuro-histopathology of the general nervous system is reported there is much ambiguity in terminology. The use of such terms as "slight increase in cellular element," "proliferation of cells" and "exudates" are common; but the term most frequently used is simply "swelling" or "edema."

INCIDENCE.

Alvarez[9] points out that neurovascular accidents are the most common disease of man. He is supported in this opinion

*This furnishes an excellent opportunity for basic research.

by Dr. James Kernohan,[10] pathologist of the Mayo Clinic. Since the neural elements of the labyrinth with its terminal circulation and the entire VIIIth nerve with its myelin sheaths are all extremely sensitive to, and expressive of, ISCHEMIC changes and edema, the incidence of neurovascular accidents in this region is, therefore, probably even greater than elsewhere in the body.

SUSCEPTIBILITY AND ETIOLOGY.

Susceptibility of neurovascular dysfunctions can no longer be regarded strictly as a disease of the aging or aged. Millman[11] reports that "More than 75 per cent of a group of 500 American soldiers killed on the battlefields of Korea showed at autopsy unmistakable signs of coronary disease. Their ages ranged from 19 to 23. Against this shocking total there was only a mere 11 per cent among the Koreans and Orientals who died under identical field conditions."

Susceptibility is divided into seven groups:

1. Inhabitants of the Western nations, mainly in the U.S.A., who consume large amounts of animal fats along with other heavy foods and are much more prone to vascular dysfunctions than the Orientals who consume mostly the plant fats and live much of their lives on a near starvation diet.*

2. Those who are most susceptible, however, in all geographic areas are the obese of *all* ages† with hypercholesteremia and diastolic hypertension (see Figs. 6 and 7).

Behnke[12] has illustrated graphically the various physical types.

A nutritional paradox exists in this country: In this land of plenty, even of the burdensome surpluses of good food, we

*Animal (saturated) fats come from all kinds of meat, especially pork, hamburgers, weiners, canned meats, gravies, commercial frying fats and canned soups. Animal fats also come from butter, whole milk, cream, cheese, (except cottage cheese), and eggs.

Plant (unsaturated) fats in high concentrations are present in corn oil (Mazola), soy oil, wheat germ oil, cotton seed, pecans, peanuts, walnuts, and other nuts. Other common food sources of unsaturated fats are olives, coconut, avocado, sweet potato, winter squash and nearly all cereals.

†I feel that juvenile hypometabolism is one of the specific causes of juvenile delinquency in both boys and girls. These children are physically ill, frequently social outcasts, often downright hostile to parents and friends and at times brutally vindictive.

are probably one of the poorest fed *overfed* nations on earth. On the patient's chart we designate this as overfed and undernourished (O.F.U.N.).

It is not uncommon to find many young executives and employed persons, as well as teenagers, whose breakfast consists only of coffee and a sweet roll, or only coffee and numerous cigarettes. These persons are naturally exhausted by

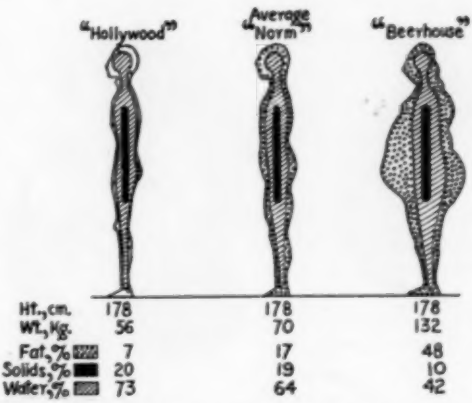

"Hollywood"
Average "Norm"
"Beerhouse"
Ht., cm. 178 178 178
Wt., Kg. 56 70 132
Fat, % 7 17 48
Solids, % 20 19 10
Water, % 73 64 42
"Nature finally dictates slimming down--Beerhouse and his brethren"
Behnke, A. R., Jr.,

Fig. 6. Beerhouse by Behnke. Hypometabolism due to obesity in the older persons.

mid-morning due to hypoglycemia so they start going to the coke machine and candy bar. This gives them a slight temporary lift but also increases the hypoglycemia. At the evening meal, as a consequence, they are starved and tend to overindulge in food, rich dessert, and beverages producing a dangerous obesity.

3. Individuals (chiefly males) who have peptic ulcer and have been forced to ingest large quantities of whole milk or half milk and half cream, which, of course, predisposes strongly to hypercholesteremia.

4. Males until middle life; thereafter, in postmenopausal or oophorectomized females, the susceptibility becomes more equally divided. This strongly suggests a gonadotropic genesis.

Masters and Ballew[13] have shown there is no significant reduction in the function of the pituitary, adrenal, thyroid or pancreas during aging—even including the eighth and ninth decades of life. The gonads are alone in their obvious and

Susan, age 14, May, 1957. Susan, age 15, Feb., 1958, less 40 pounds.

Fig. 7. Hypometabolism due solely to obesity in the very young.

well-substantiated retrogression during the fifth and sixth decades of life.*

Page,[14] former president of the American Heart Association, humorously points out that while the sex factor does not seem to have been invented primarily with the intent of preventing women from developing vascular dysfunctions until after menopause it seems to be working out that way.

5. Persons with autonomic imbalances; those with a domi-

*This suggests strongly that gonadal substitution therapy may be indicated from the climacteric (male and female) to the grave.

nant sympathetic autonomic nervous system—the get-it-done type.

6. Persons under stress, emotional reactions pre-disposing to vasospasm and its sequela.

7. Individuals with hereditary background of neurovascular dysfunctions.*

SYMPTOMS AND DIAGNOSIS.

Otologists are frequently consulted before serious neurovascular damage has occurred elsewhere. This is often due to an annoying tinnitus or just an occasional ping in the ear. A mild vertigo is frequently the reason for an ear consultation. There is no other place in the human body where a slight vascular dysfunction such as a vasospasm, a tiny embolus or a thrombosis can so quickly cause minor symptoms or, at times, such a great calamity!

Again, careful and thoughtful history is of great importance in the early diagnosis of neurovascular dysfunctions of the VIIIth nerve. Alvarez[7] has repeatedly pointed out that the physician often neglects to inquire and the "patient often fails to tell the physician of a bad dizzy spell at the start of his trouble." Tinnitus of a roaring, pounding or pulsating type and wedging as shown on many audiograms are at least presumptive evidence of a primary vascular narrowing or obstruction.

I believe the violent seizures of Ménière's disease are just as diagnostic of gradual narrowings or occlusions of the blood vessels supplying the VIIIth nerve as the pain of angina pectoris is to the narrowing or occlusion of one or both of the coronary arteries.

The *flashing of bright lights* in the outer canthus of the eye occurs less often but it is of significant diagnostic importance.

*There are now five mammalian genetic laboratories in the U. S. A. devoted to the study of genes. While many agents are involved in this investigation the endocrine glands seem to be under constant scrutiny. Someone has pointed out that misplaced egotism will probably be the biggest obstacle to applying eugenics.

Only a few routine, inexpensive laboratory procedures are required. Roentgenograms are useless.

THERAPY.*

The causes of any dysfunction or any pathologic state are the sum total of all conditions required to produce it; therapy, therefore, must be directed at the causes.

Regarding treatment, Fowler, Sr.,[1] stresses, "It is important not to be dogmatic in these matters, to say it can't be done. Keep trying with newer and newer ideas, old definitions and old concepts are not enough." Therapy is divided into three categories: nutritional, the use of pharmaceutical agents and the correction of faulty habits. The dietary treatment is extremely simple; only a question of specific patient instructions.

Nutritional.

1. Weight reduction when indicated which, of itself, lowers serum cholesterol;

2. Dietary manipulation: reduction of all fats, especially animal (saturated) fats and substitution of plant (unsaturated) fats (see Fig. 8);

3. Substitution of seafoods for the main meat course several times a week because they are low in fat, have a high iodine number and abound in minerals. Otherwise, lean meats, cottage cheese and other protein as desired;

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*All treatment must be individualized and subject to change from time to time, except the nutritional phase, which remains constant until newer scientific knowledge is available.

A completely fat-free diet is not only impractical but dangerous. Both fats are used physiologically, mainly as a source of immediate and remote energy. Patients who, without medical advice placed themselves on a fat-free diet continued to gain weight and lose strength. The addition of fats to their diet, especially in the form of plant fats, entirely reversed the process.

Moderation and balance in everything should be the motto. Too many factors and regulators of metabolism are still unknown to warrant tampering with a well balanced diet. Vegetable fats should be emphasized in most American diets, but not to the entire exclusion of animal fats.

Further information concerning the development of this regimen stems mainly from the teaching of Henry A. Schroeder of Washington University, "Mechanisms of Hypertension," published by Chas. C. Thomas, Springfield, Ill., 1957; the various writings and personal communications of William H. Masters of Washington University; Seymour H. Rinzler of Cornell University and author of "The Clinical Aspects of Arteriosclerosis," published by Chas. C. Thomas, Springfield, Ill., 1957 (p. 29), and my own experiences "Ear, Nose and Throat Dysfunctions Due to Deficiencies and Imbalances," published by Chas. C. Thomas, Springfield, Ill., 1957.

4. Elimination of refined sugar and substitution of artificial sweetening (Jelsweet). Wilder and Keys[15] have shown "Sugar only supplies calories; it has no other nutritional value, and the vitamins provided by other foods are sapped by sugar in liberating these calories."

Woolley[16] points out ". . . sugar can be shown to be antagonistic to the action of thiamine, since the thiamine requirement of an animal may be increased by raising the carbohydrate content of the diet. The reason: carbohydrates, which are not antimetabolic, can be adequately supplied by baked potatoes, whole wheat bread, cereals, fresh fruits, etc. Their carbohydrate content is more slowly digested than refined sugar—thereby keeping up a constant trickle of sugar into the blood stream and preventing hypoglycemia.

5. Elimination of all sweet desserts and beverages. The reason: persons who regularly consume sweetened desserts fail to include in their diet fresh fruits (three large servings each day are desirable) with a high content of vitamin C and minerals.* And,

6. One or two raw vegetable salads daily, luncheon and supper. Cooked vegetables as desired (see Figs. 8 and 9).

Pharmaceutical.†

Massive doses initially of B complex, especially B_6 and B_{12}, parenterally, Betalin Complex F C, (Lilly), and orally Optilets-M (Abbott), and others depending later on adequate nutrition to supply necessary vitamins and minerals.

Estrogen-Androgen Balance: These potent anabolic agents, estrogen and androgen, in a balanced combination, so well presented by Masters[18] are employed in all patients, male or female, middle life or past. Masters points out that the probable synergism of these combined steroids permits smaller

*Vitamin C deficiency produces a disturbance in the formation and maintenance of the connective tissue of the body, which supports all the blood vessels and vital organs. Obviously, therefore, a defect in this tissue could be responsible for certain allergic, hemorrhagic and other types of blood vessel and nerve diseases throughout the entire body which, so far, remain unsolved.

Neither man, monkey nor guinea pigs can synthesize vitamin C and most likely cannot store it.

†Details of the uses of most of these pharmaceutical agents have been previously reported by me.[11]

doses of each to achieve the same physiologic effect. This is probably due to protein anabolism, maintenance of nitrogen and phosphorus balance, as well as body electrolytes. Neither masculinization nor feminization with increased hirsutism was observed in this study.

Gevrine (Lederle) and Mediatric (Ayerst) seem to be the

RELATIVELY LOW SATURATED FAT AND LOW CALORIC DIET.

Food	Permitted	Avoid
BEVERAGE	Coffee, tea, skimmed milk, buttermilk, tomato juice and fruit juices.	Whole milk, cream, I mit or avoid alcoholic beverage and beverages prepared with egg yolk or fats.
BREAD	Whole wheat Staff, Pepperridge, not more than 2 slices daily—Krinko is excellent.	White bread or biscuits unless fortified flour is used. Breads prepared with egg yolk such as corn bread, muffins, butter crackers.
CEREALS	Wheat germ, Kellogg's Special K, Quaker Oats. Add 1 or 2 teaspoons of Lecithin (Leciphos) to all of these cereals.	Highly milled (not whole grain), noodles.
CHEESE	Low fat cottage.	All others.
EGGS	2 or 3 weekly, poached or boiled. (Fry or scramble in Mazola Oil or soy bean oil.)	Fried or prepared in any other form.
FAT	Vegetable, such as Mazola, safflower, or soy, in salads and cooking. Nuts.	All others, especially animal fats.
MEAT	Lean, 4 oz. ¼ pound once or twice daily or poultry. (Remove all visible fat.)	Pork, hamburger, wieners, etc., gravy, canned meats.
FISH	Broiled, roasted (remove all visible fat). Fish, all kinds. Shell fish are superior.	
POTATO	Baked, 3 each week (jacket contains valuable minerals).	Fried or potato chips.
SOUP	Vegetable, oyster, prepared fresh with skimmed milk. Meat soups only if fat is skimmed off at icebox temperature.	Soups and sauces made from animal fat and all canned soup except Campbell's bouillon and beef.
BUTTER	Spreads made from plant fat, not more than 2 or 3 pats each day unless otherwise instructed.	Ordinary butter and hardened margarine.
DESSERT	Fresh or unsweetened frozen fruit or juices, berries or melons. Use Jelsweet for all sweetening.	All sweet dessert. (See Hidden Sugars.)
VEGETABLE	All green, leafy, red and yellow. Add Brewer's yeast.	None.

NOTE: Wheat germ, Lecithin vegetable oils and Brewer's yeast (Thompson's) may be purchased at all Natural Food stores and at many food markets.

MEAL PLAN.

Breakfast	Dinner	Supper
Citrus fruit: Whole grapefruit or 5 oz. of fresh or frozen orange juice, or 2 oranges. All kinds of berries and melons or other fruit in season. Cereal. Fish, all kinds. Coffee or skimmed milk. Toast—1 slice.	Fruit or juice. Lean meat—poultry or fish. Remove all visible fat. (Small serving.) Raw vegetable salad. Beverage. Fruit dessert.	Low fat meat—fish or cottage cheese mixed with whole lemon and/or onion. Raw vegetable salad. French dressing. Fresh or frozen fruit or berries. Skimmed milk.

Sea foods or fish of some kind should be served as the meat course three times a week.

Midmorning or midafternoon: tomato juice, fruit juice, buttermilk or skimmed milk . . . substituted for the usual coffe or coke "break."

All obese persons should know that they may with safety remove undesirable fat by serving only HALF portions of a variety of well-balanced, high vitamin-mineral foods.

Suggestion: To curb that ravenous appetite: A bowl of fresh fruits, such as bananas, oranges, apricots, etc., with cereal, skimmed milk sweetened with Jelsweet one hour before luncheon or supper. You should be able to skimp or skip the regular meal.

Fig. 8. Instructional Card No. 1 for dietary manipulation given to each patient.

agents of choice. Gevrine is used chiefly in the female and Mediatric in the male.

Other hormones, such as thyroid extract, have been discontinued as therapeutic agents, except in the thyroidectomized patient—then only in very small dosages for a short period of time. When the endocrine glands are supplied with an adequate and balanced chemical media (through nutrition), I believe strongly they will secrete their own hormones.

In autonomic imbalances Bellergal Spacetabs (Sandoz) are effective stabilizers in establishing a better integration between the autonomic, glandular and vascular systems. One-half tablet should be taken morning and evening for a short period of time until the other factors of hypometabolism have been corrected.

Enzymes.

The knowledge of enzymes is undergoing such extensive basic investigations at the present time that clinical enzymology must await more fundamental research. These investigations may be a prelude, however, to an entirely new phase of medicine which will concern hypometabolism.

Anticoagulants.

Heparin is used in small dosages concurrently with and after complete vasodilation. Laboratory control of prothrombin activity is essential.

HIDDEN SUGARS IN FOOD.

Eliminate all of these foods and beverages from your diet. Substitute fresh or unsweetened frozen fruits and fresh fruit juices.

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Food Item	In Ordinary Servings
Beverages—	Colas, soda pop, root beer and most carbonated beverages contain from 3½ to 5 teaspoonfuls of sugar.
Cakes and Cookies—	Angel food, chocolate cake, donuts, etc., contain from 3 to 7 teaspoonfuls of sugar.
Candies —	Chocolate cream, Hershey bar (small), fudge (one ounce square) contain from 2 to 4½ teaspoonfuls of sugar.
Canned Fruits and Juices—	Canned apricots, peaches and stewed fruits contain from 2 to 3½ teaspoonfuls of sugar.
Dairy Products—	Ice cream, ice cream cone, ice cream sundaes contain from 3½ to 7 teaspoonfuls of sugar.
Jams and Jellies—	Apple butter, strawberry jam and various jellies (one tablespoonful) contain from one to four teaspoonfuls of sugar.
Desserts (Miscellaneous)—	Apple pie, apricot pie, cherry pie, Jello and various puddings contain from 4 to 10 teaspoonfuls of sugar.

Fig. 9. Instructional Card No. 2—Foods and beverages to be elim nated from diet.

Vasodilators.

Histamine and nicotinic acid: When the situation is urgent, as in Ménière's disease and sudden deafness, histamine, usually with heparin, is definitely the agent of choice.

Horton[19] points out that ". . . histamine given by the intravenous route causes a greater increase in blood flow to the central nervous system than any other known drug." He also believes "Histamine is a drug of choice in the management of neurovascular disturbances of the VIIIth cranial nerve

and is quite an effective agent in *edema* occurring anywhere in the body.

Mufson[20] lists the following reasons for choosing histamine: *a*. It causes the most intense and extensive erythema, *b*. It is safest because it is a natural body constituent, and *c*. It may be used in coronary—but not in asthmatic patients.

Intravenous infusions of histamine and heparin are office procedures; hospitalization is neither necessary nor desirable. The infusion, however, must be administered by nurses trained in the technique and skilled in venipuncture. Such skilled nurses are seldom available in general hospitals. The infusions require 90 minutes each, followed by 30-minute rest periods (see Fig. 10). With proper timing of appointments, a room 7½′x9′ as shown in this photograph (see Fig. 10), can easily care for six patients each work day.

MANAGEMENT OF FAULTY HABITS CONTRIBUTING TO METABOLIC DYSFUNCTIONS.

Sleep.

Adequate and restful sleep is necessary to preserve the normalcy of the neurovascular system. Sleep is one of our most useful measures in the correction of even the most serious neurovascular dysfunctions.

Phenergan (promethazine hydrochloride), an antihistamine, 12.5 mg., at bedtime is usually effectual for all types of insomniacs. Barbiturates, of which I am a bit fearful because of their cumulative effects or addiction, should be prescribed in minimal and receding dosages. Alcohol, as hard liquor in moderation, especially in the aging patient, has a mild sedative effect by its depressive action on the cortical control centers. It is a quick-acting hypnotic of short duration with vasodilator activity. There is no direct harm to the before supper or bedtime "toddy" to assure nights of sound sleep.

Lack of Physical Exercise.

Only in the most serious neurovascular dysfunctions should bed rest be prescribed and then only for a short time. Muscles

of action (exercise) give the blood vessels the helpful squeeze to speed up circulation.

Massage and heat have a distinct therapeutic value in nearly all vascular dysfunctions. A brisk early morning walk and/or a vigorous massage, by a trained masseur or masseuse with strong hands, are excellent circulatory stimulants (no gadgets or shaking tables)! A routine morning cold sponge is also an effective circulatory stimulant.

Fig. 10. Intravenous histamine room.

Tobacco.

Circulatory disturbances caused by smoking may vary from vasospasticity of the peripheral vessels by diminishing the flow of blood to complete thromboangiitis obliterans (Buerger's disease). Roth,[21] by using a special thermometer, has shown that the temperature may fall even more than 5.3° F. in the extremities.

RESULTS.

Nearly all patients had subjective improvement—especially

in general health. Many had arrestability of further functional loss. Some had subjective and objective functional improvement of the VIIIth nerve, apparently not spontaneous or coincidental. None was cured.

SUMMARY.

The important unit of medical consideration should always be the patient as a whole—the present state of his metabolism and his biologic past—not just his diagnosed disease! I believe the broad subject of hypometabolism is the most neglected phase of medicine, chiefly because there is no definitive laboratory proof of an organic lesion. By implication it could be responsible for many other metabolic and degenerative diseases which so far remain unsolved.

I concur in the conclusions of Schroeder[22] when he states, "The final answer to this prevalent disorder of our civilization cannot be predicted with certainty. There is more to be learned than has been learned in spite of the advent of *successful* therapy."

If the outlined therapy is applied when indicated, it is my conviction that we do have a treatment now that is surprisingly helpful.

The fundamental knowledge of the diagnosis and management is easily acquired and easily applied. Certainly we may all look forward with high anticipation to substantial progress in otology during the next decade—when the medical aspects of otolaryngology will be more clearly understood. We will then no longer have to give a dour prognosis to patients with VIIIth nerve lesions. The excitement and joy of growing with a problem are the great rewards of research, both clinical and basic.

With sufficient motivation by all those engaged in research and treatment—and such motivation has been demonstrated here today—the problem of VIIIth nerve dysfunction will be solved.

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COGAN'S SYNDROME.*†

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In 1945 Cogan[1] reported four cases and found a fifth[2] in the literature, of a syndrome consisting of nonsyphilitic interstitial keratitis associated with vestibulo-auditory symptoms. In 1949 he added four[3] more cases to the literature. The interstitial keratitis is usually bilateral, characterized by rapid remissions and exacerbations and may or may not lead eventually to diminution of visual acuity. The vestibulo-auditory complaints consist of severe vertigo, tinnitus, nystagmus, ataxia and progressive bilateral sensory-neural deafness, although here, too, there may be remissions and exacerbations. Complaints referring to either the eyes or the ears may herald the onset of the disease.

In discussing Cogan's syndrome only those cases that meet the afore-mentioned criteria will be considered true representatives of this syndrome; therefore, cases such as that reported by Lindsay,[4] in which the patient had iritis and vestibulo-auditory symptoms, cannot be included in the group of true examples.

Since Cogan's original papers were published, 14[4-12] additional cases of the syndrome of nonsyphilitic interstitial keratitis and vestibulo-auditory symptoms have been reported.

Our purpose in presenting this paper is: *1.* to report four additional cases of the rare syndrome of nonsyphilitic interstitial keratitis and vestibulo-auditory symptoms; *2.* to dem-

*Read at the meeting of the Middle Section, American Laryngological, Rhinological and Otological Society, Inc., Chicago, Ill., Jan. 18,-19, 1960.

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Editor's Note: This manuscript received in The Laryngoscope Office and accepted for publication Feb. 8, 1960.

onstrate, through a review of our cases and those reported in the literature, that in our opinion Cogan's syndrome is only one manifestation of a systemic disease, although most authors have considered it to be a nosologic entity; *3.* to report two atypical cases of Cogan's syndrome and to review the literature on other such examples; because through a discussion of these cases we feel that we support our argument that Cogan's syndrome is not a nosologic entity; *4.* to strengthen the hypothesis, through our cases and a review of the typical and atypical cases of Cogan's syndrome in the literature, that Cogan's syndrome, as previously proposed, is only one manifestation of periarteritis nodosa[8]; *5.* to discuss a few of the syndromes once considered nosologic entities, as in the case of Cogan's syndrome, but which were later found to belong to the group of collagen diseases; and *6.* to show a trend which could indicate that all the collagen diseases are only variants of the same basic pathologic process. All cases reported herein are from Mayo Clinic in the section of otolaryngology and rhinology.

REPORT OF CASES.

Case 1. A 20-year-old university student was first seen in the Section of Otolaryngology and Rhinology of the clinic on October 24, 1950.

On October 15, 1949, while she was attending Northwestern University, an upper respiratory infection had developed with headache and gradually developing photophobia. Two days later it was noted that the nasopharyngitis was not clearing; also, her eyes were becoming bloodshot, and she had an episode of vertigo all of which led to her hospitalization on October 19. Within three days after her admission to the hospital, severe vertigo developed associated with loss of equilibrium, rotatory nystagmus, nausea, vomiting and bilateral tinnitus which, when loudest, was associated with temporal pain. The onset of bilateral deafness was noted and was rapidly progressive. At the same time, ocular symptoms became exceedingly severe, and a diagnosis of bilateral interstitial keratitis was made. The severity of interstitial keratitis fluctuated greatly, and improvement or exacerbation in one or the other or both eyes often occurred within 24 hours. A cough usually accompanied a flare-up in her eyes.

She was dismissed from the hospital after approximately one month with complete deafness of the right ear and partial deafness of the left ear. She was able to manage with a hearing aid until January, 1950, when deafness became complete in her left ear also. On one occasion during the winter of 1950, however, although the hearing was totally absent at 7:00 P.M., it had returned sufficiently by 11:00 P.M. so that the patient could hear the telephone ring upstairs, a dog scratching on the door and an airplane overhead. She continued to have remissions and exacerbations of interstitial keratitis every few days.

From October 19, 1949, to October 24, 1950, extensive laboratory investigations had been performed. Leukocyte counts varied from 7000 per

cubic millimeter with a normal differential to 14,700 with 77 per cent neutrophils, and at no time was there any eosinophilia. The rate of sedimentation of erythrocytes (Wintrobe method) ranged from 20 to 38 mm. per hour. Urinalysis gave normal results, and values for the following factors were normal: serum proteins and albumin-globulin ratios, serum cholesterol, serum nonprotein nitrogen, carbon dioxide combining power, serum chlorides, cephalin cholesterol flocculation test, thymol turbidity, bleeding time, clotting time, platelet count and tests on the spinal fluid including chemistry studies. Results of the following tests were negative: serologic tests for syphilis, the treponema immobilization test, agglutination tests for Brucella and Proteus OX-19, and tests of urine for porphyrins. Repeated blood cultures with the use of both the aerobic and anaerobic technique did not show growth. Cultures from the vaginal secretions, throat and lacrimal fluid were negative for pathogenic organisms. Virus studies were done on scrapings from the conjunctivas, on washings from the eyes and nasopharynx, on serum and on stools, but nothing of significance was demonstrated. Roentgenograms of the thorax, teeth, hands, feet, skull and mastoid processes did not show evidence of abnormality.

During this same year she received a variety of treatments including a course of aureomycin, a one-week course of terramycin, two courses of chloromycetin, one lasting 11 days and the other 30 days; aureomycin (duomycin) was applied to her eyes; she had one intravenous injection of typhoid vaccine; antihistaminic drugs had been used, as well as a one-week course of Cortisone totaling 1100 mg., and a two-month desensitizing course of histamine. All these therapeutic measures were of no benefit, and the course of the disease remained unchanged. During the summer of 1950 the patient began studying lip reading.

On general examination at the clinic, it was noted that she had had an appendectomy in 1948. The past and family histories were otherwise noncontributory. The blood pressure was 104 mm. of mercury systolic and 68 mm. diastolic, pulse 96 beats per minute and temperature 98.4° F. She had slight ataxia, and the deep reflexes appeared hypoactive, but she would not remain for a neurologic examination.

Her vision was as follows: right eye, 6/60; left eye, 6/60. The ophthalmologists found edema of the corneas chiefly limited to the substantia propria in the central portions. The periphery of the corneas was clear except for large vessels deep in the substantia propria passing from the limbus to the edematous regions. Photosensitivity was mild in degree.

The audiogram showed essentially no hearing. The Kobrak cold caloric and Barany chair tests demonstrated no response from either labyrinth.

Urinalysis showed red blood cells, grade 1 (on the basis of 1 to 5 with 1 as the least and 5 as the greatest number) and white blood cells, grade 3 (on the basis of 1 to 4); the values for hemoglobin, erythrocyte count, leukocyte count and differential count, and the erythrocyte sedimentation rate (Westergren method) were normal. One examination of the stool for parasites, agglutination tests for Brucella, and a roentgenogram of the thorax did not show any abnormality. The roentgenogram of the skull showed evidence of slight calcification in the parasagittal meninges. The patient was given Cortisone ophthalmic ointment and dismissed on October 27, 1950, unimproved.

There is no doubt that this case is a typical example of Cogan's syndrome. The patient not only had remissions and exacerbations of the ophthalmic symptoms and signs, but she

also had a single remission of the hearing loss. There are several findings that suggest that the disease process was of widespread distribution such as the nasopharyngitis, the headache and temporal pain, the neutrophilic leukocytosis, the elevated erythrocyte sedimentation rate and the number of red and white blood cells in the urine. It is interesting to speculate on the reason for abdominal pain leading to appendectomy in 1948. Abdominal pain with subsequent appendectomy is not uncommonly seen in periarteritis nodosa, but in this case, unfortunately, we have no detailed information concerning the findings at operation.

Case 2. A 25-year-old married woman was seen in the Section of Otolaryngology and Rhinology of the clinic on February 14, 1955.

In August, 1951, bilateral interstitial keratitis had developed during the latter part of a pregnancy, and the patient was treated with Cortisone ophthalmic drops. In November, 1951, she delivered spontaneously. Approximately three months after delivery, the ocular condition had cleared spontaneously. The interstitial keratitis recurred, however, and for two months she received pyromen intravenously without any apparent benefit. She had experienced remissions and exacerbations of the ophthalmologic condition up to the time she was seen at the clinic.

In May, 1953, severe rotatory vertigo associated with nausea and vomiting and tinnitus developed. The attack lasted two weeks and subsequently the patient noticed loss of hearing in both ears. This loss had progressed gradually although on occasions she had noticed some fluctuation in her auditory acuity.

In November, 1955, the patient had been hospitalized for investigation, and a letter from her home physician stated that values obtained from study of blood chemistry, blood counts, and agglutination tests for various bacterial and viral diseases were normal. Biopsy of a lymph node revealed nonspecific hyperplasia and biopsy of a muscle did not show any abnormality. A diagnosis of nonsyphilitic interstitial keratitis with bilateral deafness was made, and she was given a course of systemic Cortisone but without benefit. The dosage was not specified in the letter.

She began to wear a hearing aid in November, 1955, which was of great help at first but which gradually became of less value, so she began to study lip reading.

Her history revealed that she had had difficulty maintaining her equilibrium in the dark and when walking, and she had difficulty focusing her eyes while driving a car. The audiogram showed almost complete loss of hearing in the right ear, some hearing being apparent at 95 decibels at the 2000 frequency. In the left ear the loss of hearing followed almost exactly the same line for total loss for speech except at the 2000 frequency where it was found to be 75 decibels. There was no recognition of phonetically balanced words in the right ear, but the percentage for phonetically balanced words in the left ear rose to about 35 per cent at 15 decibels above the threshold. On the Kobrak's modification of the cold caloric test there was no response to 30 cc. of ice water in either ear. There was no spontaneous or positional nystagmus.

Ophthalmologic examination showed that the vision without correction was 6/7+ in both eyes. In the lower portions of the corneas there were

several deep infiltrations about 1 mm. in diameter, and in the upper portions of each cornea, some distance from the upper limbus, one infiltration measured about 7 mm. in length and 1 mm. in breadth. The latter infiltrations were vascularized from above by vessels that lay in the posterior layers of the cornea. The picture was typical of that described by Cogan.

The patient was dismissed on February 15, 1955, with the diagnosis of Cogan's syndrome.

This was a typical case of Cogan's syndrome encountered at the clinic for diagnostic confirmation. The patient was not seen in a general diagnostic section, and a general history and examination were not obtained; therefore, whether or not she ever displayed any systemic manifestations throughout the course of the illness, we are unable to answer. It is interesting that the interstitial keratitis had its onset during the second half of a pregnancy.

Case 3. A 34-year-old married woman was first seen at the clinic on July 22, 1940. In 1934 she had awakened one morning with bilateral deafness, tinnitus, severe vertigo, occipital headache and a generalized warm feeling. After three months the deafness cleared spontaneously, and the tinnitus and vertigo also ceased. In 1937 the patient experienced a similar loss of hearing associated with the same complaints that had developed previously. This attack lasted six months and again cleared spontaneously. One year prior to being seen at the clinic she had a third episode of deafness and vertigo which had persisted up to the time of registration at the clinic. The attacks of vertigo seemed to concern her more than the bilateral deafness. During each episode of hearing impairment, the patient had been troubled with a productive cough. She had been treated with sulfanilamide, prontosil and vitamin B_1 without benefit. She had had a mastoidectomy on the left side in 1935. There was no history of syphilis.

The patient was 5 feet 3½ inches tall and weighed 137.5 pounds; her blood pressure was 130 mm. of mercury systolic and 78 mm. diastolic; the pulse was 106 beats per minute, and the temperature 98.8° F. A systolic murmur was heard at the apex of the heart. She had severe bilateral sensory-neural deafness as shown by the tuning-fork tests. She could not hear the 128-cycle fork. She heard the 2048-cycle tuning fork for 15 seconds less than did the examining physician. Results of the Rinne test were positive bilaterally, and those of the Weber test did not indicate lateralization. She could not hear a watch with either ear.

Examination of the eyes showed her vision to be as follows: right eye, 6/60; left eye, 6/20. There was bilateral deep scarring of the corneas, ghost vascularization of old interstitial keratitis and scattered small areas of healed chorioretinitis which was more marked in the right eye than in the left eye.

The results of urinalysis and the values for hemoglobin and leukocytes were normal. Roentgenograms of the thorax and sinuses were normal. The basal metabolic rate was minus 3 per cent. The Kline, Kahn and Kolmer flocculation tests gave negative results. The Hinton flocculation test was doubtfully reactive and was not considered significant. The patient was dismissed on July 24, 1940.

This patient displayed dramatic fluctuations in loss of hearing. There were not many indications of a systemic disease process, those recorded being only productive cough, occipital headache and generalized warm feeling during the episodes of hearing impairment. It is impossible to say whether or not the systolic heart murmur had been present prior to the onset of the disease. As in Case 2, the history and examination, unfortunately, were not complete.

Case 4. A 25-year-old married woman was first seen at the clinic on September 9, 1958. On December 3, 1957, when she was one month pregnant, a buzzing sound developed in both ears. She was given nicotinic acid and after 24 hours the tinnitus stopped. It occurred again one month later but again stopped after 24 to 48 hours. Each month she had a similar episode of tinnitus until March, 1958, when she had an attack of rotatory vertigo associated with nausea while she was in a grocery store; the attack lasted half an hour. In April she had a second similar attack of vertigo while attending a movie. The vertiginous attack persisted for three days. From this time until her delivery on July 31, 1958, she had more frequent attacks of vertigo associated with nausea and tinnitus. Her delivery was spontaneous and uneventful. On August 11 a severe attack of vertigo associated with vomiting developed. She was hospitalized and sedated with promazine hydrochloride (sparine) for 36 hours. At this time she began to notice bilateral loss of hearing and aching over both cheeks. After one week she was dismissed from the hospital. During her pregnancy she had been on a low-sodium diet and from the initial appearance of tinnitus she had been taking 100 mg. of nicotinic acid four times a day.

The patient's loss of hearing was progressive, and on August 28, 1958, she was rehospitalized for further investigation. At this time the results of general examination were within normal limits and neurologic examination showed that she had a mild type of locomotor ataxia. An audiometer test showed a sensory-neural type of hearing loss of 55 decibels on the left and 45 decibels on the right. Response to the caloric tests bilaterally was completely absent.

The erythrocyte sedimentation rate (Westergren method) was 35 mm. in one hour and the value for protein in the spinal fluid was 64.3 mg. per 100 cc. Urinalysis showed 6 to 10 red blood cells and 7 to 10 white blood cells per high-power field. Laboratory investigation, including values for hemoglobin, hematocrit reading, leukocyte count and differential count, blood serology, fasting blood glucose, serum urea, total serum protein and albumin-globulin ratio, serum sodium, serum potassium, carbon dioxide combining power, serum chlorides, a complete study of the spinal fluid, an electrocardiogram and roentgenograms of the thorax and skull, gave results or evidence that was within normal limits. She was placed on a regimen of 80 mg. of prednisone (meticorten) a day for one week. After two days of therapy she noticed some improvement in her hearing. On September 5, an audiogram revealed 20 to 25 per cent improvement in each ear. She was dismissed from the hospital on September 6 and began decreasing the dose of meticorten by 5 mg. each day.

When first seen at the clinic on September 9, 1958, it was noted that she had had severe urticaria during her first pregnancy. The results of neurologic examination were negative except for hearing impairment and ataxia. The neurologists did not feel that the value for spinal fluid

protein of 64.3 mg. per 100 cc. found elsewhere was significant so a lumbar puncture was not done.

Her vision was 20/20 for both eyes; the results of ophthalmoscopic examination were negative. The audiogram showed:

Frequency	125	250	500	1000	2000	4000	8000	10,000
AC—Left	10	15	20	20	25	55	0	0
AC—Right	30	30	35	30	30	65	0	0

The bone-conduction curve closely paralleled the air-conduction curve in each ear. Evidence of distorted hearing of the type seen in disease of the cochlear end-organ was manifested by slight recruitment of loudness in the right ear over that in the left ear, threshold of pain at 90 decibels in the right ear and 95 decibels in the left ear, and 10 per cent reduction of discrimination for speech as the signal intensity was increased 15 decibels above the level of most comfortable loudness.

Caloric tests showed essentially complete lack of response of both labyrinths. Urinalysis showed 8 white blood cells per high-power field; the leukocyte count was 13,500 per cubic millimeter of blood with 84 per cent neutrophils. The concentration of hemoglobin, erythrocyte count and roentgenograms of the thorax and skull, including Stenver's view, were within normal limits. Skin sensitization tests and cytologic examination of a cervical smear gave negative results.

The patient was dismissed on September 12, 1958, with the diagnosis of toxic labyrinthitis.

One week after her dismissal the patient discontinued the use of meticorten and subsequently noticed an increase in the loss of hearing. She was hospitalized in her home town for several days, and her hearing deteriorated to complete bilateral deafness.

On September 18 rotatory vertigo, nystagmus, lacrimation on the left side, photophobia, ptosis and rhinorrhea developed. Although she had no vertigo from that time on, complaints involving the left eye and the nose persisted. She was again hospitalized and treated with kenacort eye drops four times a day and with four intravenous injections of histamine without any benefit.

On October 11 she woke up with a sharp "catching" pain over the lower left costal margin both anteriorly and posteriorly. This pain was aggravated by deep breathing, changes in position, lying on her left side and walking. The same day a dull ache developed in her left shoulder and extended into her neck, with nausea and vomiting which were not associated with vertigo. At this time the leukocyte count was 15,000 per cubic millimeter of blood; the erythrocyte sedimentation rate was 49 mm. in one hour and her temperature was 101° F. Thereafter she had episodes of the same pains associated with nausea. On October 16, 1958, she returned to the clinic and was admitted directly to the hospital. On her admission the blood pressure was 120 mm. of mercury systolic and 90 mm. diastolic; her pulse was 104 beats per minute and the temperature, 99.5° F. There was tenderness over the left border of the cervical portion of the trapezius muscle, the lower left ribs posteriorly and the left costovertebral angle. She was still moderately ataxic.

The audiogram showed the patient to be almost completely deaf. She reported that she felt speech at 90 to 95 decibels but she was unable to understand speech at any intensity. On delayed feedback tests, there was no change in the rhythm or quality of her speech.

Examination of the eyes showed narrowing of the left palpebral fissure. The left conjunctiva was slightly hyperemic. Keratitis involved a wedge-shaped portion in the inferior nasal quadrant of the left cornea. The cloudiness in this portion was mild and mostly stromal.

The laboratory investigation included several determinations for erythrocyte sedimentation rate (Westergren method) which varied from 114 to 77 mm. per hour and a leukocyte count of 11,000 per cubic millimeter of blood with a normal differential count. There was no eosinophilia at any time. An electroencephalogram showed a general disturbance of function without evidence of lateralization. The concentration of hemoglobin, erythrocyte count, urinalysis, urinary determinations for porphyrins, determinations for calcium, phosphate, total protein, albumin-globulin ratio and urea in the serum, L.E. clot test, serologic tests for syphilis, blood tests for Toxoplasma antibodies, an electrocardiogram, studies of spinal fluid and roentgenograms of the thorax and lumbosacral portion of the spinal column were all within normal limits.

On October 19 the patient had aching pain and slight tenderness in the muscles of her right calf, but no nodules for biopsy were noted. On October 21, under the assumption that this was periarteritis nodosa with Cogan's syndrome as a local manifestation, the patient was placed on a daily dose of 200 mg. of Cortisone orally and 2.5 per cent hydrocortisone ophthalmic drops every two hours. On October 24 the patient's muscle pains were gone, and she was feeling better. She received 5 cc. of milk intramuscularly on October 26, 5,000,000 typhoid bacilli intravenously on October 28 and 15,000,000 on October 30. On October 28 it was noted that the stromal infiltration of the left cornea was almost completely gone. The patient's temperature had varied from 96° to 100.5° F. since admission and always spiked during the afternoon.

During the night of November 1, 1958, chills and cramping, burning pain developed in both of the patient's legs. There was some diffuse tenderness over the leg muscles. On November 2 her temperature spiked to 103.4° F. and excruciating pains developed in both legs. Large doses of narcotics and packing her legs in ice were required to relieve the pain. After two days, when the severe pain had ceased, an electromyogram was made in an effort to find a suitable region for biopsy. There was no abnormality of nerve conduction or of response to needle electrode examination and, in view of this, blind biopsy was not attempted.

On November 6 it was noted that the patient's left eye was almost normal and that she had only slight discomfort in her legs. Improvement continued, and she was dismissed on November 8, 1958, on 200 mg. of Cortisone daily. A follow-up letter on November 25, 1958, revealed that she had had one flare-up of the interstitial keratitis which lasted two days but that she was showing some evidence of general improvement.

This case of Cogan's syndrome is unusual in that only unilateral interstitial keratitis had developed. The patient displayed involvement of multiple systems with diffuse muscle aches, pains and tenderness, a pleuritic type of pain, bilateral peripheral neuritis, nasal complaints, a spiking temperature which, on one occasion, reached 103.4° F., electroencephalographic abnormalities, and several other abnormal laboratory findings.

From the time of her second visit to the clinic, it was our

impression that we were dealing with periarteritis nodosa, and we treated her for this condition. The patient's hearing improved early in the course of the disease when she was given meticorten; her subsequent complete loss of hearing when the medication was discontinued seemed to indicate that the gluco-corticoids can be beneficial if given early in the course of the disease. As in Case 2, this patient's trouble began during pregnancy.

In this case the disease impressed us as one which was confined not only to the ear and eye but rather as a disease process affecting many systems, the manifestations of which were subject to remission and exacerbation and produced an unrelated picture of systemic disease not unlike that seen in periarteritis nodosa or disseminated lupus erythematosus. In order to substantiate our opinion, we reviewed the cases encountered at the clinic in which the disease has been considered to be Cogan's syndrome.

COMPARISON OF CASES.

Of the four cases we have reported, we feel that Cases 1 and 4 tend to indicate that Cogan's syndrome is only a local manifestation of a more generalized disease process. Unfortunately, Cases 2 and 3 were not thoroughly investigated and it is impossible to say whether or not more generalized symptoms and signs such as were seen in Cases 1 and 4 were ever exhibited.

In a further attempt to correlate the systemic findings in our cases with any that have occurred in previously reported examples, Table I was made. It shows manifestations that tend to indicate that Cogan's syndrome is only one of the manifestations of a systemic disease. Table I shows the 23 reported cases and our additional four cases with symptoms, signs and laboratory findings. The findings characteristic of Cogan's syndrome such as vertigo, nausea and vomiting associated with vertigo, nystagmus, loss of equilibrium, abnormal responses to caloric tests, sensory neural deafness and interstitial keratitis were omitted from Table I.

Symptoms and signs that seemed to be related to the disease

TABLE I.

Findings in Cases of Cogan's Syndrome Other Than Those Characteristic of the Disease.

Case No. and Author Reporting	Symptoms, Signs and Laboratory Findings.									
	Gastro-intestinal Tract	Nervous system including eye and ear	Cutaneous	Lymphoid tissue, spleen, liver	Musculo-skeletal system	Respiratory tract	Genito-urinary tract and urinalysis	Cardio-vascular system	Blood tests	Miscellaneous data
1. Mogan and Baumgartner[2]			Profuse perspiration left side of body							
2. Cogan[1] (Case 1)				Hepatomegaly					Leukocytosis; 6% eosinophils	
3. Cogan[1] (Case 2)		Earache in left ear					Alubumin (3+) and white blood cells in urine		Leukocytosis	
4. Cogan[1] (Case 3)	Ptomaine poisoning just prior to onset								Leukocytosis; 5% eosinophils	
5. Cogan[1] (Case 4)						Bronchopneumonia; "coldsore" in nose			Leukocytosis; 6% eosinophils	
6. Cogan[1] (Case 5)				Lymphadenopathy 1 mo. prior to onset	Stiff neck 1 mo. prior to onset	Sore throat 1 mo. prior to onset		Rheumatic fever 2 yrs. prior to onset; grade-3 systolic murmur and cardiomegaly	Leukocytosis; elevated sed. rate of erythrocytes; 28% eosinophils	Lost 30 lbs. in 8 mo. prior to onset; biopsy deltoid muscle negative

7. Cogan[1] (Case 6)	Appendectomy 5 mo. after onset					Leukocytosis	
8. Cogan[1] (Case 7)						Leukocytosis	
9. Cogan[1] (Case 8)			Stiff neck 1 mo. prior to onset			Leukocytosis	
10. Rosen[5]	Nausea; vomiting		Dull nuchal ache and tightness around neck	Cold and cough 3 mo. prior to onset		Leukocytosis	Fatigue and loss of weight during 3 mo. prior to onset
11. Robson[6]							
12. Lindsay and Zuidema[4] (Case 1)							
13. Lindsay and Zuidema[4] (Case 2)				Hemoptysis	Palpitation; pain in chest; enlarged heart		
14. Lindsay and Zuidema[4] (Case 3)							
15. Donald and Gardner[2]	Nausea, vomiting	Drowsiness; 2 convulsions; EEG showed diffuse organic changes	Pain and stiffness of neck	Severe respiratory infection 2 mo. prior to onset			Generalized fatigue

TABLE I (Continued).

Case No. and Author Reporting	Symptoms, Signs and Laboratory Findings.									
	Gastro-intestinal Tract	Nervous system including eye and ear	Cutaneous	Lymphoid tissue, spleen, liver	Musculo-skeletal system	Respiratory tract	Genito-urinary tract and urinalysis	Cardio-vascular system	Blood tests	Miscellaneous data
16. Oliner and Co-authors[8]	Nausea; vomiting; diarrhea, melena; abdominal pain and tenderness		Purpuric lesions, maculo-papular rash, subcutaneous nodules	Lymphadenopathy; splenomegaly		Pleural friction rub		Heart murmur; enlarged heart	Leukocytosis; 6% eosinophils; anemia; reversed A/G ratio; blood culture—hemolytic streptococcus	Fever; biopsy—periarteritis nodosa
17. Stevens[9]		Absence of patellar reflex		Generalized lymphadenopathy 3 mo. prior to onset		Sore throat			Leukocytosis; 8% eosinophils	Fever
18. Boyd[10] (Case 1)	Diarrhea	Drowsiness		Diffuse lymphadenopthy; splenomegaly; hepatomegaly	Stiffness of neck	Cough				Fever
19. Boyd[10] (Case 2)	Diarrhea; abdominal cramps	Drowsiness		Cervical lymphadenopathy; splenomegaly and hepatomegaly 3 mo. prior to onset	Pain in legs; backache			Tenderness along carotid and femoral vessels	Leukocytosis; 6% eosinophils	Fever; biopsy 2 muscles, negative

20. Crawford[11] (Case 1)	Nausea; vomiting; diarrhea; melena; abdominal tenderness; paralytic ileus	Frontal headaches; toxic psychosis; bilateral Babinski sign; positive Kernig's sign; cerebrospinal fluid—53 cells per cc.	Erythematous rash over palms of hands	Cervical and axillary lymphadenopathy	Nuchal rigidity; generalized muscle aches and pains	Cold 1 wk. prior to onset; acute pharyngitis and rhinitis	Testicular tenderness; urine—8-10 red and 3 white blood cells per high-power field; granular casts, and albumin		Leukocytosis; elevated blood sugar	Fever; necropsy—periarteritis nodosa
21. Crawford[11] (Case 2)		Headaches; neuralgia of Vth cranial nerve			Muscle and joint pains; nodules in muscles of extremities	Pharyngitis	Albuminuria (slight); casts in urine	Elevated blood pressure	Leukocytosis	Fever; biopsy—periarteritis nodosa; loss of weight
22. Crawford[11] (Case 3)	Massive hemorrhage	Occlusion of central vein with secondary optic atrophy			Joint pains	Cold(?); ulcerating lesions of mouth and throat	Albuminuria	Elevated blood pressure; systolic heart murmur	Leukocytosis; anemia; 45% prothrombin time; reversed A/G ratio	Fever
23. Quinn and Falls[12]		Severe frontal and temporal headaches			Migratory and generalized pains	Severe upper respiratory infection	Albumin (2+), myriads of red blood cells in urine	Grade-1 systolic apical murmur	Leukocytosis; anemia; elevated sed. rate of erythrocytes; C-reactive protein 5 to 6+; 2 blood Kahns 4+; abnormal electrophoretic curve	Fever; biopsy skin and muscle negative; persistent lassitude and fatigue

TABLE I (Continued).

Case No. and Author Reporting	Symptoms, Signs and Laboratory Findings. Gastro-intestinal Tract	Nervous system including eye and ear	Cutaneous	Lymphoid tissue, spleen, liver	Musculo-skeletal system	Respiratory tract	Genito-urinary tract and urinalysis	Cardio-vascular system	Blood tests	Miscellaneous data
24. Cody and Williams* (Case 1)		Headache; temporal pain				Nasopharyngitis; cough associated with flare-ups in eye	Urine—red blood cells, grade 1; white blood cells, grade 3		Leukocytosis; elevated sed. rate of erythrocytes	
25. Cody and Williams* (Case 2)										Biopsy—negative
26. Cody and Williams* (Case 3)		Occipital headache				Productive cough		Systolic apical murmur		Generalized warm feeling
27. Cody and Williams* (Case 4)	Nausea; vomiting	Peripheral neuritis; abnormal EEG			Nuchal rigidity; pain and tenderness in shoulder; left costal margin, leg muscle	Pleuritic pain; rhinorrhea	Urine—6-10 red blood cells per high-power field; 7-10 white blood cells per HPF		Leukocytosis; elevated sed. rate of erythrocytes	Fever

*Present paper.

and preceded the onset of complaints involving the eyes and ears were included in Table I. These included unexplained attacks of abdominal pain, lymphadenopathy and upper respiratory infections which either preceded the onset of the syndrome, with a complete remission before the eyes and ears were affected, or were the initial complaints but were still present at the onset of the characteristic features of the syndrome. Whether these forerunners of the syndrome were part of the same disease, were the factors responsible for precipitating the disease, or were just coincidental occurrences, we cannot say with absolute assurance; but the evidence suggests that these early symptoms and signs are only a few of the manifestations of a systemic disease subject to fluctuation.

In only five of the 27 cases (Cases 1, 11, 12, 14, 25) there were no significant findings other than interstitial keratitis and damage to the VIIIth cranial nerve (see Table I). On the other hand, in 13 cases there were multiple additional symptoms, signs and laboratory findings. Other findings included leukocytosis in 18 cases; involvement of the respiratory tract in 15, of the nervous system in 12, of the musculoskeletal system in 11 and of the gastrointestinal tract in ten; fever in nine; involvement of the cardiovascular system in eight and of the genitourinary system in seven; and lymphadenopathy in six.

One patient died[11] and at necropsy, periarteritis nodosa was found; in two other cases biopsy yielded evidence to substantiate the diagnosis of periarteritis nodosa.[5,11] In our fourth case and in three other instances[10,11] the diagnosis of periarteritis nodosa was made on clinical grounds. It was Oliner and associates[8] in 1953 who first suggested that Cogan's syndrome might be only a localized manifestation of periarteritis nodosa.

Of the five cases with no findings other than those characteristic of Cogan's syndrome, apparently only Cases 1, 11 and 12 were thoroughly investigated (see Table I). The report of Case 14 is short with no mention of a general history and examination, and it is impossible, as it is in Case 25, to say

whether or not any manifestations of systemic disease ever were present.

In the nine cases in Table I in which minimal additional findings such as leukocytosis, eosinophilia, and abnormal findings in the urine or an upper respiratory infection were reported, there is not enough evidence to say that manifestations of a generalized disease actually were exhibited. At least such manifestations were suggested. Thorough investigations were reported in six of the nine cases (Cases 2, 3, 4, 5, 8, 9), although we do not know just what the ptomaine poisoning immediately prior to the onset of Cogan's syndrome in Case 4 entailed (see Table I). In Case 13 examination seemed to have been complete, but the presentation is short and laboratory findings are not mentioned. There is no indication that thorough investigation was made in either Case 7 or Case 26, and we do not know the circumstances in Case 7 leading to appendectomy five months after the onset of the illness. From the reports available in these two cases (Cases 7 and 26) we have no way of knowing whether any further features indicative of a more generalized disease process were ever manifested.

In the remaining 13 cases in Table I (Cases 6, 10, 15-24, 27) it is our opinion that we have sufficient findings, other than those characteristic of Cogan's syndrome, to consider them as examples of a generalized disease process. In Table I, therefore, the evidence seems adequate for us to state that in 13 or 48 per cent of the cases of Cogan's syndrome thus far reported, the disease process is one of generalized distribution.

In nine cases there are findings that seem to indicate that the disease is not confined to the cornea and VIIIth cranial nerve, while in the remaining five cases there were no manifestations other than those characteristic of Cogan's syndrome.

In reviewing the cases of Cogan's syndrome and related conditions encountered at the clinic, we found two cases which seemed to be examples of Cogan's syndrome except for ophthalmologic findings which were not typical of Cogan's syndrome.

REPORT OF CASES OF ATYPICAL COGAN'S SYNDROME.

Case 5. A 33-year-old man was first seen at the clinic on January 1, 1956. During the late summer of 1952, a lesion had developed on the patient's right ankle followed by the development of eczematoid dermatitis of his legs and arms. He received X-ray therapy for this condition during September and October. In early October an upper respiratory infection developed, accompanied by severe pain low in the back and by headache. Following the upper respiratory infection a suspected industrial accident occurred in which cutting oil was supposed to have accidentally irritated both of his eyes. A diagnosis of conjunctivitis was made at this time. The eye condition rapidly grew worse, and the patient was hospitalized with severe uveitis and corneal ulceration. Near the end of October dizziness and impairment of hearing developed, the latter progressing rapidly in one week to total bilateral deafness. He was treated with an unknown quantity of Cortisone and ACTH.

In December, 1952, he was again admitted to the hospital with uveitis and meningismus. An acute hemorrhage developed in the gastrointestinal tract while he was in the hospital. Eleven transfusions were required and subsequent roentgenograms revealed a small ulcer on the lesser curvature of the stomach. He gradually improved in the hospital and was dismissed in March, 1953. At that time his vision, uncorrected, was as follows: right eye, 20/50; left eye, 20/30. He was totally deaf and showed no response to the caloric test. The edema, redness and photophobia gradually cleared, and in 1954 he was able to go back to work in a machine shop.

In March, 1955, redness, edema and photophobia of both eyes again developed and from that time until he was seen at the clinic, he had frequent remissions and exacerbations of his ocular condition. The use of neosone ophthalmic ointment seemed to be of benefit during the exacerbations.

The general history and examination revealed that the patient had not had symptoms of ulcer since the gastric hemorrhage in 1952. For the previous 15 years he had been troubled with allergic rhinitis consisting of lacrimation, rhinorrhea and sneezing during the months of September and October. He weighed 155 pounds and was 70 inches tall; his blood pressure was 100 mm. of mercury systolic and 58 mm. diastolic; his pulse was 80 beats per minute and temperature, 98° F. An axillary furuncle and slight benign prostatic hypertrophy were noted. The dermatologist stated that there were multiple nevi over the upper part of the chest, the back and the upper part of the arms, but poliosis or vitiligo was not evident. The audiogram showed complete bilateral sensory-neural deafness. Neither spontaneous nor positional nystagmus was present. Kobrak's modification of the cold caloric test resulted in a minimal response bilaterally, the response being slightly more active on the left side.

The ophthalmologist stated that the patient had sclerosing keratitis, and although the disease in the patient's eyes was rather severe, he still had remarkably good vision. Vision in the right eye measured 20/60; in the left eye, 20/25

The results of urinalysis were normal and values for hemoglobin, erythrocyte sedimentation rate and erythrocyte count were normal. The leukocyte count was 11,600 per cubic millimeter of blood and the Kline flocculation test was nonreactive. A roentgenogram revealed no abnormality in the esophagus, stomach, or duodenum. The patient was dismissed on January 20, 1956.

In this case vestibulo-auditory findings characteristic of

Cogan's syndrome were displayed, but the conjunctivitis, superficial keratitis, uveitis, and sclerosing keratitis were not typical of the syndrome. Involvement of multiple systems in the disease process was displayed during the early stages. These findings consisted of dermatitis, upper respiratory infection, pain in the back, headache, meningismus and leukocytosis. We do not know how much Cortisone and ACTH the patient had received prior to the appearance of the massive gastric hemorrhage and, therefore, cannot be certain whether or not this treatment was responsible for the gastric ulcer.

In this paper the term "atypical Cogan's syndrome" is defined as a condition with vestibulo-auditory manifestations and ocular findings that include keratitis, uveitis, episcleritis and others but not interstitial keratitis.

Case 6. A 22-year-old farmer was first seen at the clinic on July 11, 1956. Between 1950 and 1952 the patient had episodes of an appearance of a lump below the lobe of the right ear associated with small sores over the pinna. These episodes lasted about one week and recurred two or three times a year.

In the spring of 1952 redness, soreness, burning and lacrimation of both eyes developed. These symptoms cleared spontaneously but recurred again in 1953, and from that time on the patient had experienced remissions and exacerbations of the ocular complaints. The soreness and burning in his eyes during exacerbations were frequently sufficiently severe to keep him awake at night. Cortisone drops brought relief while they were used.

Biopsy of a cervical lymph node was done in 1952, but the reasons for this examination and the findings were not available. In 1953 the patient was treated for a duodenal ulcer at which time he had epigastric pain relieved by the ingestion of food. He had no further trouble during the two years prior to being seen at the clinic.

Early in 1954 the patient was working on a tractor when severe rotatory vertigo associated with nausea and vomiting developed. The episode lasted three days. Approximately two weeks later he had a similar attack of vertigo, but this time bilateral tinnitus also developed, louder in the right ear than in the left. Within the next month he began to notice impairment of hearing in his right ear. The attacks of vertigo continued but gradually became less severe. In June, 1954, he began to notice impairment of hearing in his left ear. For the next year he noticed fluctuation in his ability to hear. From March, 1955, until the patient was seen at the clinic, he had been free of vertiginous attacks but tinnitus had persisted. The patient noticed that his voice was hoarse during the onset of impairment of hearing.

On examination the patient weighed 119.5 pounds; he said that he had lost 15 pounds in the previous three years. The blood pressure was 130 mm. of mercury systolic and 68 mm. diastolic, pulse 64 beats per minute and temperature 97.8° F.

An audiogram showed a 40 to 65 decibel loss in both ears. The loudness balance test showed essentially symmetric increase of loudness. On

the speech reception test in the right ear at 70 decibels, 15 decibels above threshold, the patient had 55 per cent of the words correct. In the left ear at 70 decibels, 20 decibels above threshold, he had 55 per cent of the words correct. On the Kobrak equilibrium test there was no response to 30 cc. of ice water.

Examination of the eyes showed perilimbal injection on the left and a minimal and isolated patch of perilimbal injection on the temporal side of the right limbus. A small disruption of epithelium of the inferior nasal quadrant of the cornea and two disruptions of corneal endothelium were noted immediately below the center of the cornea of the right eye. Palpebral conjunctivitis was bilateral. The ophthalmologist's opinion was that the patient did not have the typical interstitial keratitis seen in Cogan's syndrome but that he had a condition more like episcleritis.

Results of urinalysis and values for hemoglobin, erythrocyte count, leukocyte count and erythrocyte sedimentation rate were normal. Results of the serologic tests for syphilis also were negative. Roentgenograms of the head and thorax were without evidence of abnormality; a roentgenogram of the stomach showed evidence of a duodenal ulcer. The patient was placed on an ulcer diet, and systemic treatment with Cortisone under the supervision of his home physician was advised. He was dismissed on July 18, 1956.

All features of Cogan's syndrome except those for typical interstitial keratitis were present in this case. In our opinion, however, this case had to be classified as an atypical example of Cogan's syndrome in the same manner as Lindsay and Zuidema's[4] case with bilateral iritis (see Table II). The presence of many manifestations such as cervical lymphadenopathy, sores on the right ear, hoarseness associated with loss of hearing, loss of weight and duodenal ulcer suggested that the disease process was of widespread distribution.

These three examples of what we considered to be atypical Cogan's syndrome led us to wonder whether or not other such cases had been reported in the literature and, if so, what diagnosis, either clinical or histologic, had been given by their authors.

REVIEW OF THE LITERATURE.

We were able to find seven cases in the literature, in addition to our Cases 5 and 6, that showed characteristics of Cogan's syndrome or could be considered as atypical examples of the syndrome. In five of the nine cases in Table II, a diagnosis was made of periarteritis nodosa[13-17]; in one case the diagnosis was disseminated lupus erythematosus,[18] in one case, Cogan's syndrome,[4] and in our two cases atypical Cogan's syndrome. Cases 1, 2, 3, 5, 7, 8, and 9 (see Table II) are close-

TABLE II.

Cases Showing Some of the Characteristics of Cogan's Syndrome.

Case No. and Author Reporting	Involvement.			Diagnosis
	Eye	Auditory	Vestibular	
1. Middleton and McCarter[13]	Failing vision right eye; left eye poor from injury 9 years before; pupils did not react to light.	Bilateral deafness; bilateral tinnitus.	Dizziness; nystagmus.	Periarteritis nodosa.
2. Bernstein[14]	Three to four attacks of amblyopia in left eye; occlusion of left central retinal artery.	Bilateral deafness.		Periarteritis nodosa.
3. McNeil and associates[15]	Drooping right eyelid.	Bilateral deafness; bilateral tinnitus.	Vertigo.	Periarteritis nodosa.
4. Ingalls[16]	Bilateral uveitis and keratitis.			Periarteritis nodosa.
5. Spiegel[17]	Episcleritis; iritis; periorbital swelling, right eye.	Bilateral deafness;		Periarteritis nodosa.
6. Macrae and O'Reilly[18]	Loss of visual acuity; mild papilledema of fundus; exudates and hemorrhages.	Bilateral tinnitus.	Vertigo.	Systemic disseminated lupus erythematosus.
7. Lindsay and Zuidema[4]	Bilateral iritis and secondary glaucoma of left eye.	Bilateral deafness; bilateral tinnitus.	Vertigo; bilateral hypoactive caloric response.	Cogan's syndrome.
8. Cody and Williams* (Case 5)	Bilateral conjunctivitis, superficial keratitis, uveitis, sclerosing keratitis.	Bilateral deafness	Dizziness; bilateral minimal caloric response.	Atypical Cogan's syndrome.
9. Cody and Williams* (Case 6)	Bilateral episcleritis.	Bilateral deafness; bilateral tinnitus.	Vertigo; bilateral absence of caloric response.	Atypical Cogan's syndrome.

*Present paper.

ly related to Cogan's syndrome and probably can be considered atypical examples. It is interesting to note that the diagnosis in four of these cases was periarteritis nodosa, and in our cases findings were suggestive of a systemic condition. Case 4 is representative of the eight cases reported by Cogan[19] of periarteritis nodosa and corneoscleral lesions; however, Parker and Kernohan[20] pointed out that when periarteritis nodosa involves the nervous system, any clinical syndrome may be produced, and this is especially applicable to the eye.[21] Harris and associates,[22] in an analysis of 101 reported cases of periarteritis nodosa, found that 23 per cent of the patients had visual disturbances and that changes such as papilledema, exudates and hemorrhages in the fundus are not necessarily a result of hypertension but may be due to the arteritis itself as exemplified by two of the reported cases. Case 6 is included to draw attention to the role of disseminated lupus erythematosus in lesions of the eye. Baehr and co-authors[23] found that 12 of 23 patients having disseminated lupus erythematosus had abnormalities of the fundus; he stressed that these changes were the result of essential vascular pathologic conditions in the retina. It has been pointed out that, just as in periarteritis nodosa, but less commonly, all the layers of the eye may be involved in disseminated lupus erythematosus.[21]

In the literature, reports of cases of collagen diseases with sensory-neural deafness resulting from arteritis are rare; the cases of periarteritis nodosa with perception deafness are included in Tables I and II.

In Table I a significant number of patients having Cogan's syndrome showed manifestations that are highly suggestive of systemic disease. In our cases and in those reported in the literature these manifestations are frequently seen to undergo remissions and exacerbations which produce a rather unrelated clinical picture. In seven of the 27 cases in Table I a diagnosis of periarteritis nodosa was made on histologic or clinical grounds. Seven cases in Table II can be considered as atypical examples of Cogan's syndrome. In four of these seven cases a diagnosis was made of periarteritis nodosa, and in two, manifestations suggested that the condition was of a systemic nature. It was pointed out that although few cases

of sensory-neural deafness in collagen diseases are reported in the literature, it is not unusual to find lesions involving practically all structures of the eye in periarteritis nodosa, disseminated lupus erythematosus, or even in rheumatoid arthritis.[12,24]

In conclusion, therefore, we feel it is justifiable to say that Cogan's syndrome is not confined to the cornea and VIIIth cranial nerve but rather that it is only one manifestation of a systemic disease—a systemic disease that on occasions involves so many seemingly unrelated structures and produces such a bizarre clinical picture that one cannot help but link it with the collagen diseases; also, from the available evidence, it would seem that the syndrome could be included in the group with periarteritis nodosa. In the discussion of the paper by Quinn and Falls,[12] Norton expressed the opinion that the relatively good prognosis and the frequent failure of biopsy of muscle to yield a diagnosis were two important objections to the hypothesis that Cogan's syndrome is only a local manifestation of periarteritis nodosa.

There are many cases of periarteritis nodosa reported in the literature, such as the case of Cury and associates,[25] in which the patients have lived six or more years with the disease. Grant,[26] in a review of the literature up to 1941, drew attention to patients who had survived from four to 32 years and felt that in many of the other cases in which the duration was reported to be much shorter, the onset of disease might have been considerably antedated by taking into account previous similar illnesses reasonably regarded as expressions of periarteritis nodosa. Weiss[27] stressed that the disease is not invariably fatal and that the prognosis would improve with earlier clinical recognition of the disease. Rose and associates,[28] in 1950, estimated that at least 5 to 10 per cent of patients recovered and they, along with Spiegel[17] and Ragan,[29] stressed that the prognosis depended upon the extent of involvement of the vital organs. If the arterial lesions heal, and in the process do not infarct a vital area, the patient will recover, and no clue to the basis of the illness will be available; therefore, when angiitis is discussed, it probably includes only a small portion of the total group with the disease, and the

selection definitely includes a large number of patients with fatal disease.

In Cogan's syndrome, although the disease is systemic, lesions of vital organs are usually of minor importance, and from the available evidence it would appear that because Cogan's syndrome has a relatively favorable prognosis, an association with periarteritis nodosa is certainly not negated.

The uncertainty of random biopsy of muscle in yielding a diagnosis in periarteritis nodosa and the necessity of repeated biopsies is well documented in the literature,[26,28,29] and it is generally accepted that negative findings on biopsy do nct rule out the possibility of periarteritis nodosa. Rose and associates[28] described four cases which contained necropsy reports of periarteritis nodosa. Even though multiple biopsies had been performed in two cases and a single biopsy in two cases, yet a diagnosis of periarteritis nodosa had been confirmed on microscopic examination in only one instance. It is certainly evident, therefore, that negative results on biopsy in Cogan's syndrome do not rule out the possibility of periarteritis nodosa.

Klinge[30,31] was the first to introduce the concept that a group of systemic diseases affects connective tissue. Klemperer and associates[32] introduced the term "collagen diseases" to indicate the site of the characteristic lesion in these diseases, and under this term he[32-34] included rheumatic fever, rheumatoid arthritis, polyarteritis nodosa, acute disseminated lupus erythematosus, generalized scleroderma and dermatomyositis. Since the origination of the term "collagen diseases," many syndromes once considered separate entities seem to fit either partially or entirely into this group of diseases. Such is the case in Libman-Sacks syndrome,[35,36] idiopathic midline granuloma,[19,37-42] temporal arteritis,[39,43,44] Loeffler's syndrome[28,39,45-47] and thrombotic thrombocytopenic purpura.[21,35] It is not surprising, therefore, to see Cogan's syndrome identified with the collagen diseases.

Just as these syndromes, previously considered as separate entities, are being grouped together under the broad term "collagen disease" and present a somewhat clearer picture to

the clinician, so the individual members of this group seem to be more closely related. As the volume of literature on the respective collagen diseases grows, it is increasingly evident that we are not finding a clearer differentiation between one and the other, but that we are discovering more overlapping on the histologic, clinical and experimental levels.

The term "collagen diseases" refers to the fact that alterations of the extracellular portions of the connective tissue are prominent and systemic in these diseases,[33] and the changes may be degenerative or proliferative. Both the degenerative and proliferative alterations terminate frequently in sclerosis with or without hyalinization.[48] It was Banks'[36] impression that the vascular lesions in many of the collagen diseases were similar and that some cases begin as one and terminate as another. He wondered whether all of them had the same denominator.

Mallory[49] pointed out that the collagen diseases merged with one another so frequently that it was extremely difficult to separate them. He stated that at the Massachusetts General Hospital and elsewhere, there had been a great many cases of clinically typical disseminated lupus erythematosus that showed widespread periarteritis nodosa at necropsy, and this also was true of rheumatic fever and dermatomyositis.[50] He felt that there were no histologic findings pathognomonic of disseminated lupus erythematosus. In support of this, Baggenstoss[51] cited a case in which there were typical skin lesions of disseminated lupus erythematosus and the L.E. cell phenomenon in the bone marrow but which showed widespread arterial lesions indistinguishable from those observed in typical cases of periarteritis nodosa.

Ball[52] reported cases showing that the arteritic changes found in the rheumatoid patient all fall within the histologic variants of polyarteritis nodosa, and he felt that the arteritis of rheumatic fever was only another histologic variant. Dowling, with Griffiths[53] and alone,[54] and Brock[55] stated that the early cutaneous, muscular and vascular changes in scleroderma and dermatomyositis show precisely the same alterations though they vary in degree in individual cases.

Pagel and associates[56] emphasized the general involvement of the vascular system as the underlying cause of the muscular and dermal changes in dermatomyositis although they said that these changes were not specific for this disease as they were also seen in scleroderma and rheumatoid arthritis. Later, Pagel[39] stated that the basic vascular changes in periarteritis nodosa, disseminated lupus erythematosus, dermatomyositis, scleroderma, "arteritis granulomatosa allergica," and temporal arteritis are similar, if not identical, although there are differences in the frequency and distribution of the lesions in the different diseases.

Ellman and Ball,[24] Pirani and Granville,[57] and Macrae and O'Reilly[18] drew attention to the morphologic similarities between the lesions of rheumatoid arthritis, rheumatic fever, periarteritis nodosa, disseminated lupus erythematosus, scleroderma and dermatomyositis, and Pirani and his co-worker[57] stated that though fibrinoid degeneration is less frequently seen in rheumatoid arthritis, scleroderma and dermatomyositis, they run a more chronic course and pathologic findings in early stages are scarce. These are only a few of the many references in the literature which seem to show that all collagen diseases have the same basic vascular alterations, the differences being only in degree and distribution.

The literature contains numerous reports of cases which displayed either clinically, histologically, or both, the characteristics of two or more of the collagen diseases. Ophüls[58] in 1923 stated that one did not have to study many cases of periarteritis nodosa to discover its close relation to the rheumatic diseases, and he drew attention to the similarity between granulomas in periarteritis nodosa and rheumatic nodules. Since then others[13,59] have re-emphasized this impression. There are many examples[17,18,22,28,45,60-63] in the literature of an association of rheumatic fever and periarteritis nodosa in an individual patient, and in 1956, Rose[64] estimated that 12.5 per cent of cases of polyarteritis nodosa showed evidence of past or active rheumatic fever. Periarteritis nodosa also has been seen in association with rheumatoid arthritis,[52,55,65-67] with findings characteristic of both rheumatic fever and rheumatoid arthritis,[66,68] with disseminated lupus erythematosus,[40,50,51]

and with findings characteristic of both disseminated lupus erythematosus and rheumatoid arthritis.[49] Disseminated lupus erythematosus has occurred in patients having rheumatic fever,[18,69] rheumatoid arthritis,[29,35,70] scleroderma[36,71] and dermatomyositis[36,72] and in patients with findings characteristic of both rheumatic fever and dermatomyositis.[73] The similarities between dermatomyositis and scleroderma have been mentioned. Dermatomyositis has been seen in patients with rheumatic fever[74] and scleroderma in patients having rheumatoid arthritis.[24]

With an overdosage of desoxycorticosterone acetate to rats, Selye and associates[75,76] were able to produce polyarteritis nodosa, nephrosclerosis, myocardial and joint lesions similar to those associated with acute rheumatic fever, and in some instances lesions were reminiscent of the proliferative stage of scleroderma.

Two laboratory procedures should be mentioned briefly. The L.E. cell phenomenon is a useful test in the diagnosis of disseminated lupus erythematosus; however, the recent literature has shown that it is not a completely specific one. As previously mentioned, Baggenstoss[51] cited a case in which the L.E. cell phenomenon had developed in the bone marrow, but histologically it was typical of periarteritis nodosa. A sizable proportion of patients with rheumatoid arthritis have positive L.E. cell tests[29,66] and there are examples in the literature of false-positive L.E. cell phenomena occurring in diseases such as miliary tuberculosis.[77]

The second group of procedures to be considered is the serology tests for syphilis which occasionally are found to give falsely positive results in both disseminated lupus erythematosus[78,79] and periarteritis nodosa.[28,80] We are not in a position to state the significance of these falsely positive reactions to serology tests, but it is of interest that they occur in both of these conditions.

We made no attempt to review all of the voluminous literature on the collagen diseases, and from the available information it is impossible to make any dogmatic statements. It would seem, however, that we have been able to demonstrate

a trend indicating that all of the collagen diseases have a common basic pathologic relation in the vascular system that is molded, through constitutional or other unknown factors, into the patterns of syndromes and diseases known today as individual members of the collagen group of diseases.

SUMMARY.

There have been 23 cases of Cogan's syndrome reported in the literature, and we have reported an additional four cases. Of these four cases, a clinical diagnosis of periarteritis nodosa was made in one instance, and in two cases there were findings which seemed to indicate that Cogan's syndrome is only a local manifestation of a more generalized disease.

Of the entire 27 cases of Cogan's syndrome 13, or 48 per cent, had sufficient findings other than those characteristic of Cogan's syndrome to be considered examples of a generalized disease process. In nine cases features were present that at least suggested that Cogan's syndrome is a generalized disease. Five cases showed no findings other than those characteristic of the syndrome. In three cases a diagnosis of periarteritis nodosa was made histologically and in four cases, clinically.

We reported two cases of atypical Cogan's syndrome with features indicating that each was a generalized disease process. Five additional cases of what seemed to be atypical Cogan's syndrome were found in the literature, and in four of these cases a diagnosis of periarteritis nodosa had been made.

We concluded that Cogan's syndrome is not confined to the cornea and VIIIth cranial nerve, but that it is only one manifestation of a systemic disease. From the available evidence, it would seem that this systemic disease is periarteritis nodosa.

The relatively good prognosis and the frequent failure of muscle biopsy to yield a diagnosis are not serious objections to the hypothesis that Cogan's syndrome is only a local manifestation of periarteritis nodosa.

It is now generally considered that Libman-Sacks syndrome, idiopathic midline granuloma, temporal arteritis, Loeffler's

syndrome and thrombotic thrombocytopenic purpura also may be identified with collagen diseases. We have shown a trend which could indicate that all collagen diseases have a common pathologic basis in the vascular system which is moulded through constitutional or other unknown factors into the patterns of syndromes and diseases that are known today as individual members of the collagen group of diseases.

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OTOLOGICAL FUNCTIONAL MICRO-SURGERY POST GRADUATE COURSE.

A practical course of surgical techniques in otological surgery will be conducted by Dr. Michel Portmann at the University of Bordeaux, France, Ear, Nose and Throat Department, June 26 to July 5, 1960. This course will be given in English.

The number of assistants will be limited to twenty, divided into two groups. The fee of $100.00 is to be paid at the Faculty of Medicine of Bordeaux, at the beginning of the course. Applications should be sent to Dr. Michel Portmann, 45 Cours Foch, Bordeaux, France.

ACOUSTIC TRAUMA OF THE COCHLEA FROM EAR SURGERY.*†‡

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It is now well established that high energy acoustic signals delivered to the cochlea can cause tissue damage which is usually most severe in the region of the upper basal turn, and is manifested functionally by deafness most severe for high frequencies. A classical clinical example is found in patients exposed to a single, or repeated, air borne blast of high intensity (as from musketry, fire crackers, explosions).

It has been shown recently that a blow to the head results in a similar mechanical insult to the cochlea, having its greatest impact likewise on the upper basal turn.[12]

Case 1. Mr. X. A 29-year-old male salesman was involved in an automobile accident, following which he was unconscious for an hour and had discharge of blood and cerebrospinal fluid from the right ear. On regaining consciousness, he complained of hearing loss in the right ear. He reported having experienced good hearing prior to the accident. Roentgenograms revealed a longitudinal fracture of the right temporal bone. The next day there was a moderately severe combined conductive and sensory-neural hearing loss and drainage of serohemorrhagic fluid from the right ear. An audiogram taken four months later showed persistence of the sensory-neural deafness. There was a slight hearing loss in the midfrequency range and a profound loss for frequencies above 2000 cps (see Fig. 1-a).

The evidence from an animal experiment should have finally dispelled the common misconception that the deafness follow-

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*Read at the meeting of the Middle Section, American Laryngological, Rhinological and Otological Society, Inc., Chicago, Ill., Jan. 18-19, 1960.

†This work was supported in part by a Grant from the Central Bureau of Research of the American Otological Society and in part by Grant B-1909 of the Public Health Services.

‡The high-speed motion pictures referred to in the text have been made possible through an equipment loan with the Office of Naval Research. Nonr. 1893(00).

Editor's Note: This manuscript received in The Laryngoscope Office and accepted for publication Feb. 8, 1960.

ing a head blow could be the result of VIIIth nerve or brain injury.[13] The hearing deficits, as well as the spatial distribution and histopathological appearance of the cochlear lesions of animals subjected to head blows, were identical to those resulting from the discharge of a 32 caliber cartridge near the ear.[8]

Cat 1. Ches. The right ear was destroyed and baseline behavioral pure tone thresholds were taken. The animal was

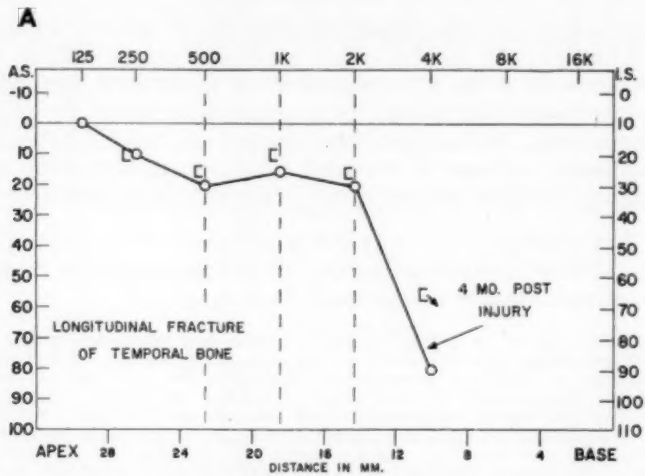

Fig. 1-a. Case 1. Audiogram showing hearing loss existing four months following head injury. The cochlear injury is the result of so-called "inner ear concussion."

anesthetized, the skull exposed by a midline scalp incision, and a blow delivered to the left temporoparietal area of the skull. The scalp incision was closed with silk sutures. Auditory testing was resumed two days after administering the head blows, and the animal was tested about every four days until sacrificed on the 22nd day.

Postoperative behavioral audiograms revealed a moderate hearing loss for frequencies up to 2,000 cycles, a profound loss for 4,000 and 8,000 cycles, and near normal hearing for

16,000 cps. The auditory thresholds improved over a two-week period, after which they remained stationary, with the final audiogram at the end of three weeks showing a persisting 4,000 and 8,000 cps dip.

On histological examination there was a loss of outer hair cells from 7.75 to 10.5 mm. region. The degree of injury varied considerably in the ten cats in this series, but in all cases the maximum injury occurred in the region of the upper basal turn, which is the region of maximum importance for the frequencies 4,000 to 8,000 cps (see Fig. 1-b).

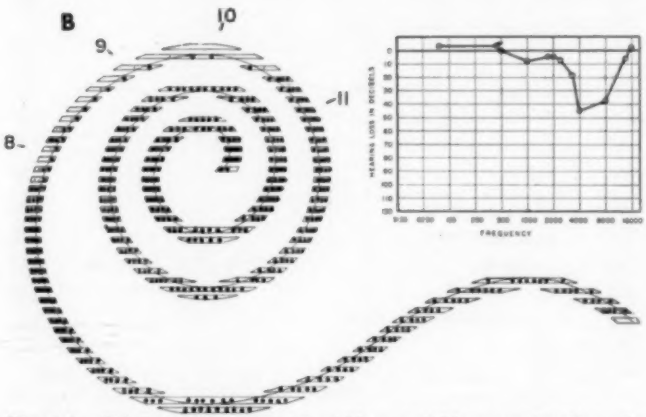

Fig. 1-b. Cat 1. Audiogram and cochlear graphic reconstruction of cat following blow to the head. There is a loss of hair cells in the 7.5 mm. to 10.5 area of the upper basal turn which has resulted in a 4000 and 8000 cps hearing loss.

It is obvious that a blow to the head can result in a bone conducted acoustic signal of sufficient magnitude to injure the organ of Corti.

The concept that surgical procedures can create acoustic energy of sufficient magnitude to cause cochlear injury is not new. The improper use of the mallet and gouge in exenteration of sclerotic mastoid bone can create such an injury.

Case 2. B.B. This nine-year-old boy had a chronic draining left ear since the age of one. There was a perforation in Shrapnell's membrane with a foul smelling discharge. The pars tensa was intact.

At operation (1949) the mastoid cortex was removed with mallet and gouge. Many firm blows were used to accomplish proper exenteration. The cell partitions were removed with an electrically driven burr. The epitympanic space was widely exteriorized because of cholesteatoma.

The postoperative course was satisfactory except that there was a sensory-neural type hearing loss for frequencies above 2,000 cps (see Fig. 2-a).

Ruedi and Furrer[11] have produced similar high frequency hearing losses (temporary) in human volunteers by reflecting

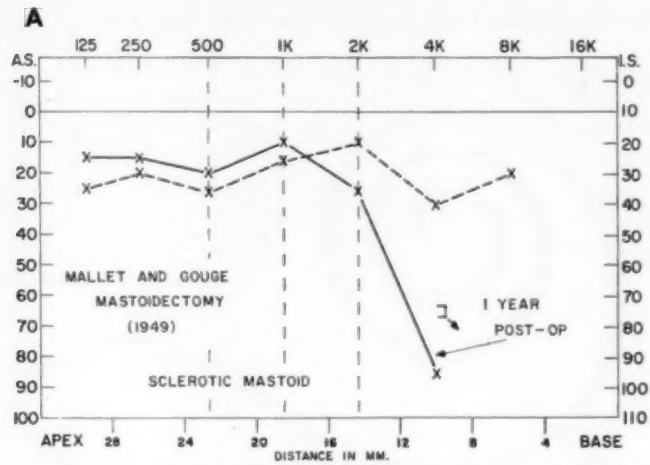

Fig. 2-a. Case 2. Pre- and postoperative audiograms showing high frequency hearing loss resulting from mastoidectomy.

the scalp over the mastoid bone and delivering mallet blows directly to the bone.

In many human surgical procedures and in a series of 60 cats in which electrically driven burrs (cutting, polishing, and diamond) were used, there have never been hearing deficits attributable to acoustic stimulation. Apparently, the acoustic intensities generated by the burr are at safe levels. This might not be true if the burrs were applied directly to any part of the intact ossicular chain.

It is becoming increasingly apparent with the development

of new surgical procedures, that there is more danger of acoustic injury to the cochlea. In tympanoplasty procedures, for example, a number of potentially injurious maneuvers may be performed: *e.g.*, palpation of various parts of the ossicular chain; incision of the incudostapedial joint; removal of granulations, connective tissue bands, and hyalinized collagen (tympanosclerosis) from the stapes or round window areas; repositioning the ossicles on the stapes; placing the pars tensa or a skin graft on the stapes; inadvertently

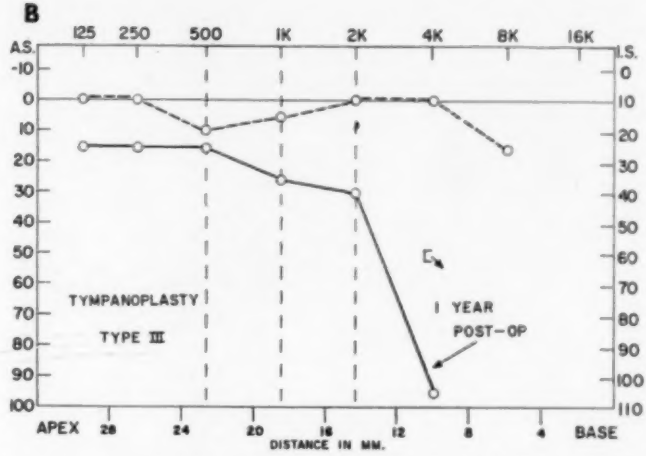

Fig. 2-b. Case 3. High frequency hearing loss secondary to stapes manipulations occurring in the course of middle ear surgery.

striking the stapes with an instrument; etc. This kind of surgical complication is demonstrated by the following case:

Case 3. V.B., No. 933792. This 25-year-old school teacher had intermittent suppuration from the right ear for five years. There was a large perforation of Shrapnell's membrane.

At operation, squamous epithelium was found to line the epitympanum, envelope the head of the malleus and body of the incus, and extend into the anterior mesotympanum. The pars tensa was intact. To accomplish complete removal of the squamous epithelium, it was necessary to remove the incus and the head of the malleus. The pars tensa was mobilized partially and depressed to make contact with the head of the stapes. After appropriate surgical preparation, the epitympanum and mastoid

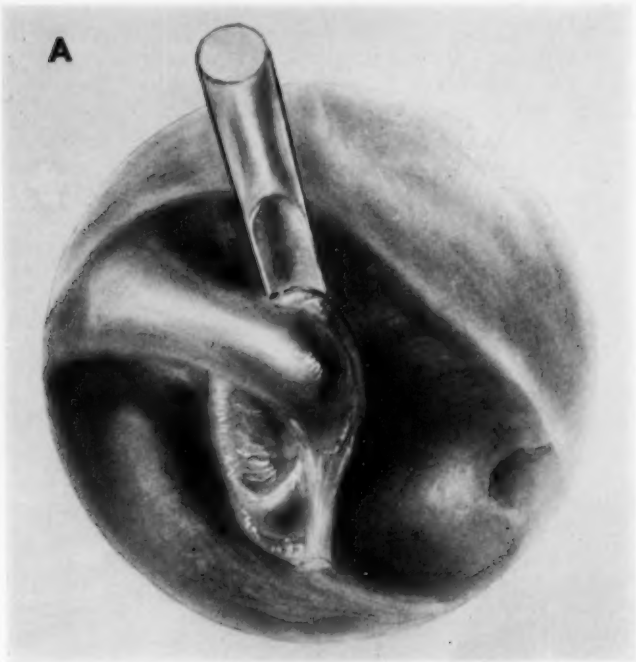

Fig. 3-a. Drawing showing chisel located at the anterior margin of the footplate as formerly commonly used for stapes mobilization.

antrum were covered with a free split-thickness graft from the inner surface of the arm.

The postoperative course was satisfactory. Although the bone-air gap in the speech range was about 15 db, the ear sustained a severe sensory-neural hearing loss for frequencies above 2,000 cps. The injury apparently was secondary to stapes movements coincident with removal of the incus and repositioning of the pars tensa (see Fig. 2-b).

Stapes operations for otosclerosis are even more apt to create cochlear damage. The stapes is often manipulated drastically with a variety of picks and chisels designed to accomplish mobilization (see Fig. 3-a). After mobilization, the intact stapes is often rocked back and forth, or pushed in and out of the oval window, creating amplitudes of movement which are enormous (in comparison to physiological move-

ments). The sudden mobilization of an ankylosed footplate or the maneuvers to remove an intact footplate probably create similar intense stimulation. Following is an example of such a case.

Case 4. E.P., No. 054776. The history and findings were typical for bilateral otosclerosis. At operation, the anterior one-third of the footplate was found to be involved in the otosclerotic lesion. The head, neck and crura were removed by disarticulating the incudostapedial joint and pushing the stapes toward the promontory so as to break the crura at

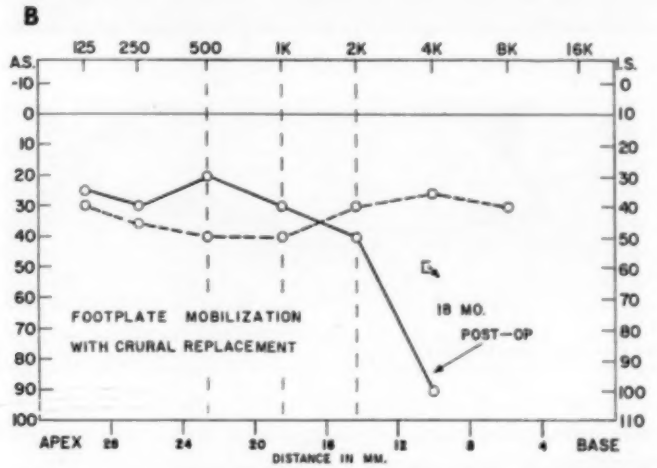

Fig. 3-b. Case 4. High frequency hearing loss resulting from extensive manipulation of the stapes footplate.

their bases. The posterior two-thirds of the footplate was then manipulated with small needles and chisels until separated and free at all margins. A tantalum wire prosthesis was then interposed between the incus and mobilized portion of the footplate.

The hearing gain for speech frequencies was unsatisfacory, but in addition there was a severe sensory-neural loss for frequencies above 2,000 cps. Apparently, the operative manipulations of the footplate were of such magnitude as to damage the cochlea (see Fig. 3-b).

The nature of the cochlear injury resulting from stapes manipulation has been demonstrated in an experiment on stapes fracture in cats.[14] Of 12 ears with experimental fractures, there was operative displacement of the large part of the footplate in four. In one of these, the footplate was

subluxated out of the oval window and in this ear the saccule and cochlea remained normal. In the other three the displacement of the footplate fragment was inward but probably not so far as to come in contact with the saccule. In these the saccular wall was ruptured and the organ of Corti damaged in the upper basal level and/or lower middle turns. Protocols for these animals follow.

Cat 2. Jo, left. Using a postauricular approach and aseptic technique, the crura were fractured from the footplate and a small needle was used to perforate the center of the foot-

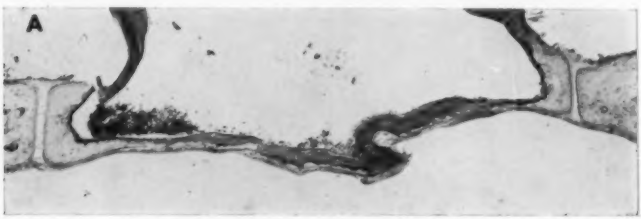

Fig. 4-a. Cat 2. Experimental fracture through the central portion of the footplate. Sacrificed three months later. a—The stapes footplate showing complete bony healing, following comminuted fracture of its midportion.

plate. Postoperatively, no nystagmus or ataxia was apparent. Sacrificed in three months.

Histological examination showed a comminuted fracture of the footplate healed by profuse bony regeneration. There was a rupture of the saccule with collapse of its wall onto the underlying neuro-sensory epithelium which appeared normal. The other vestibular sense organs appeared normal. There was injury and partial loss of outer hair cells of the organ of Corti in two anatomically separated areas, one in the upper basal turn from 9.5 mm. to 10.2 mm. and the other in the lower middle turn from 11.5 mm. to 12 mm. (see Figs. 4-a, 4-b, and 4-c).

Cat 3. Til, right. By an aseptic operation through a postauricular approach, the oval window area was exposed and the crura were fractured from the footplate and removed. A

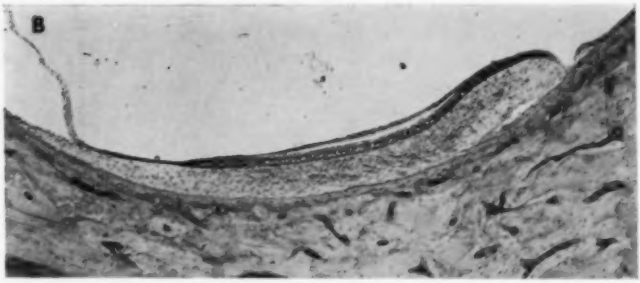

Fig. 4-b. Cat 2. Rupture and collapse of the saccular wall.

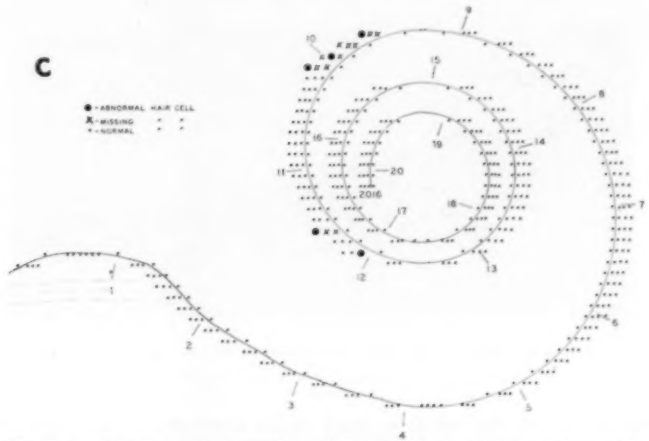

Fig. 4-c. Graphic reconstruction of the cochlea showing hair cell loss in the upper basal and lower middle turn.

fine needle was used to dislocate the anterior margin of the footplate and depress it into the vestibule. In this maneuver, the anterior three-fourths of the footplate fractured from the posterior one-fourth, (which remained in its normal position). Subsequently, the mobilized section returned near its normal location in the oval window. Sacrificed in three months.

Histological study revealed a linear vertical fracture extending through the posterior part of the footplate. There

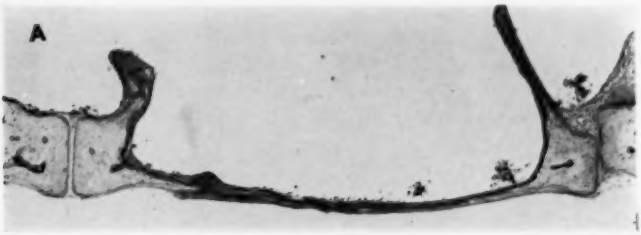

Fig. 5-a. Cat 3. Fracture dislocation of the anterior two-thirds of the stapes footplate. Sacrificed three months later. a.—View of the footplate showing slight inward subluxation of the anterior two-thirds. There is bony healing of the fracture located at the junction of the posterior and middle thirds of the footplate.

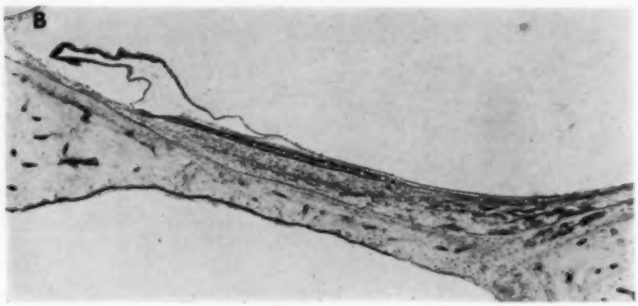

Fig. 5-b. Cat 3. Rupture and collapse of the saccular wall.

was a tear in the saccular wall and a decrease in the hair cell population of the saccular macula. The other vestibular sense organs appeared normal. There was moderate injury to the organ of Corti involving the outer hair cells in two distinct regions of the upper basal turn, between 7 mm. and 9 mm. and between 10.5 mm. and 11 mm. (see Figs. 5-a, 5-b, 5-c, and Fig. 6-b).

Cat 4. Ji, left. By an aseptic operation through the post-auricular approach, the oval window area was exposed, and the crura were fractured from the footplate and removed. A fine needle was used to depress the anterior margin of the footplate. A linear fracture occurred at the junction of the

middle and posterior thirds of the footplate, with the anterior two-thirds being depressed into the vestibule. This anterior segment remained in this depressed position. There was some escape of perilymph which was controlled with the application of a small piece of gelfoam. Sacrificed in three months.

Histological examination showed that the anterior two-thirds of the footplate was slightly depressed into the vestibule. The gap at the stapediovestibular joint anteriorly was

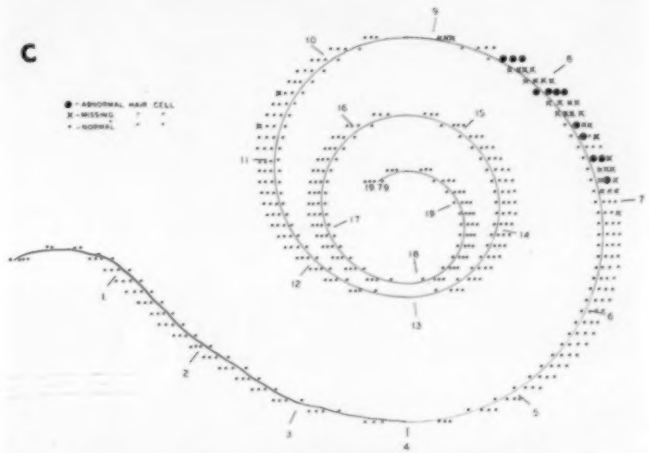

Fig. 5-c. Cochlear reconstruction showing severe loss of hair cells in the upper basal turn (see Fig. 6-b).

healed by a thin two-cell layer thick membrane, and the fracture line was firmly healed by new bone formation. There was a tear in the saccular wall and a decrease in the hair cell population of the saccular macula. The other vestibular sense organs appeared normal. There was moderate injury to the organ of Corti involving the outer hair cells in the region of the upper basal and lower middle turns between 10 mm. and 12 mm. (see Figs. 7-a and 7-b).

McCabe and Lawrence[9] found tears and collapse of the saccular walls, as well as cochlear damage, in a high percentage of guinea pig ears subjected to high intensity noise.

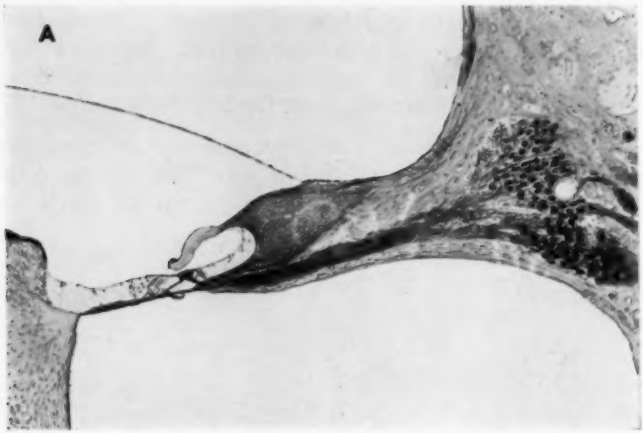

Fig. 6-a. View showing loss of outer hair cells of the organ of Corti in the upper basal turn, following an experimental blow to the head.

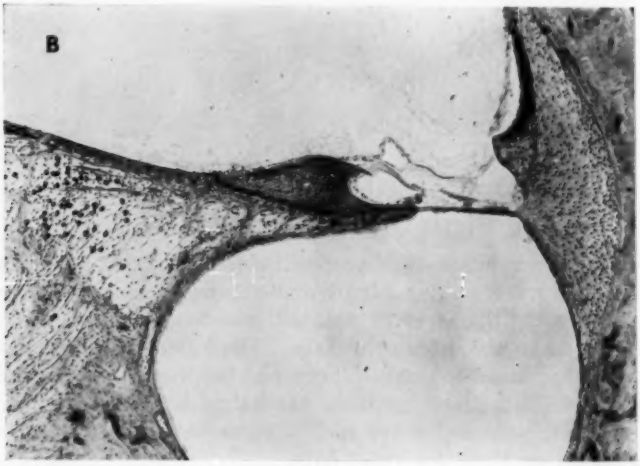

Fig. 6-b. Injury to the upper basal turn of the cochlea of Cat 3, showing rupture and collapse of Reissner's membrane, extensive damage to the organ of Corti, and secondary degeneration of spiral ganglion. (See graphic reconstruction, Fig. 5-c.)

In their animals, as in ours, there was no injury to the utricle and semicircular canals. They suggested that this finding supported the concept of a functional dichotomy between the pars superior (utricle and canals) and pars inferior (saccule and cochlea).

There are two factors common to the injuries described in the foregoing: *a.* the lesions are confined to the region ap-

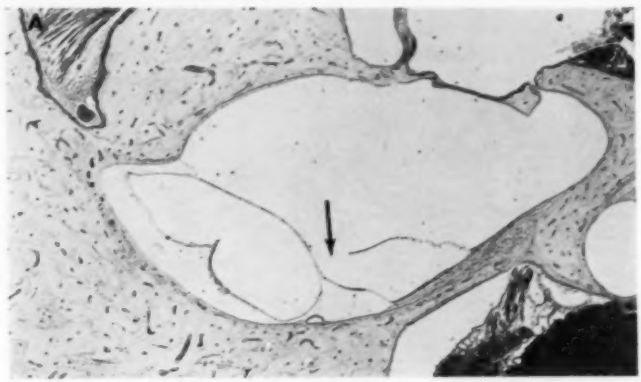

Fig. 7-a. Cat 4. Inward displacement of the footplate of the stapes. Sacrificed in three months. a.—Low power view showing inward subluxation of the anterior two-thirds of the footplate and rupture of the saccular wall (Arrow).

proximately 8 to 12 mm. from the basal end of the cochlea; and *b.* they have been caused by single blast-like acoustic events (or by their bone-conducted equivalents). Such events are commonly referred to as *transients.* This statement necessitates a brief description of acoustic transients and of the cochlear response thereto. After describing it first in 1933, Bekesy had termed the latter phenomenon the *traveling bulge.*

Much of the following is derived from experiments on cochlear models built according to Bekesy's specifications. Such models provide an excellent opportunity for studying mechanical events as they are most likely to occur in actual cochleae. Very often interpretation of purely mechanical cochlear func-

tions are made easier by the fact that these models, for instance, do not have a cochlear nerve attached to them. Their enlarged size permits visualization of the equivalent of events which themselves cannot be demonstrated in the ear by means of other presently known methods. Although ample evidence has been accumulated to the effect that qualitatively speaking such models are good replicas of the ear, quantitative interpretation of their results is somewhat more difficult.

Fig. 8 gives an example of the simplest case of an acoustic

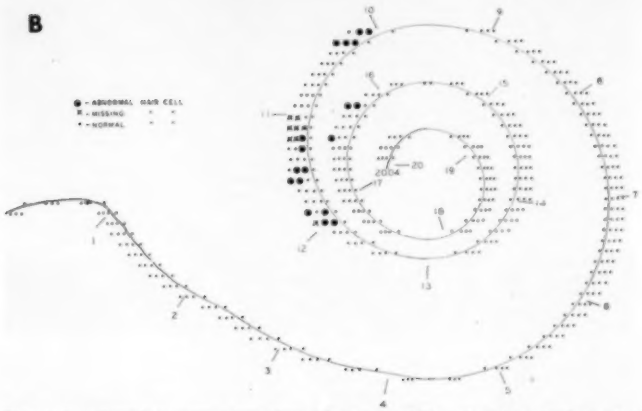

Fig. 7-b. Graphic reconstruction of the cochlea showing lesion of the organ of Corti in the 10 mm. to 12 mm. region.

transient: a (gradual) step function. Shown are *a.*—the time course of the applied signal; *b.*— its spectrum; and *c.*— the response of the model, *i.e.*, the traveling bulge and its envelope. It is noted that the envelope does not duplicate the signal spectrum. Spectrumwise, amplitude is inversely related to frequency, whereas the bulge forms a definite maximum along the partition. The position of this maximum along the partition varies with the inverse time constant of the signal. For brief time constants it is somewhat nearer the windows and vice versa.

This brief description may suffice to indicate the difficulty

one faces when trying to explain the observations of cochlear injuries caused by stapedial manipulations (Figs. 3 - 7). Although accurate data are not available, the motions of the footplate caused by such manipulations are likely to have relatively long time constants. Even if one assumes that such injuries occur when the stapes footplate is broken loose (which appears quite logical), whereby the "snap" releases a large

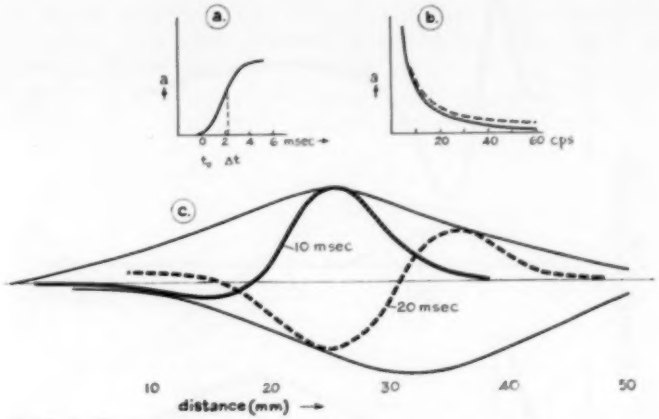

Fig. 8. Transient response of cochlear model. a.—Time course of signal: gradual step function. At time t, amplitude is gradually stepped up. The time constant (Δt), the time at which 63 per cent of ultimate amplitude is reached, is commonly used for definition of time courses.

b.—Spectrum of above transient (solid line) and of an instantaneous step function (dotted line). The product of time constant and band-width approximates unity. Therefore, band-widths of signals with longer time constants are more restricted than those of signals with short time constants. These spectra are of the continuous broad-band type.

c.—Envelope over traveling bulge containing two instances of the bulge at an earlier (10 msec.) and at a later time (20 msec.). The envelope shown described only the maximum amplitudes of the first crests, positive and negative.

amount of energy quite suddenly, the involved time constant can hardly be expected to be sufficiently short to produce a bulge with significant displacement amplitudes along the basal portion of the partition. The only point in which such stimuli stand out is their large amplitude. At such occasions, stapedial amplitude may approach 1 mm. Compared to that at the threshold of hearing (stapedial amplitude approximately 3×10^{-10} cm. for a 1,000 cps signal) that is indeed an extremely

large value. The notion had been expressed in an earlier communication[10] which was based upon some preliminary data that there might be a trading relationship between the inverse time constant and amplitude so that amplitude might make up for long time constants. A number of parameters concerning cochlear fluid motion were examined in an effort to find such a trading relationship, yet in the end none was detected;

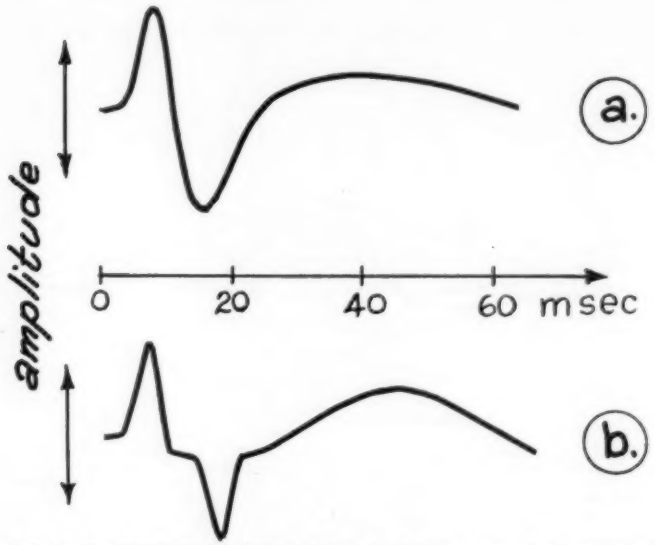

Fig. 9. Displacement patterns with time at the 27 mm. point along the partition. a.—without amplitude limitation; b.—with amplitude limitation of the applied signal. In high-speed motion picture films the spatial separation of the positive and negative peaks became quite noticeable.

therefore, as an alternate solution, the possibility of *nonlinear* distortion was considered.

It is doubtful that the inner ear can follow very large amplitudes in a linear manner. The elastic limitations of the annular ligament, if still present, and/or those of the round-window membrane are likely to be exceeded. An amplitude limitation of the original window displacement is not simply followed by a like occurrence of the displacement pattern along

the partition. Since the displacement of the cochlear partition is 90° ahead in phase of the original window motion,[15] the ensuing phase alteration results in a *center-clipping* of the traveling bulge. Fig. 9 shows the displacement pattern of a point about halfway along the partition before and after amplitude limitation of the applied signal. (It is noted in this drawing that displacement is plotted *vs.* time in contrast to that of Fig. 8 in which it had been plotted *vs.* distance.) The center clipping effect is quite obvious. As a matter of fact when high speed motion picture films were taken of traveling bulges at the beginning of the present work on transients, a few such center clipped bulges had been produced inadvertently. They were not recognized as such until the

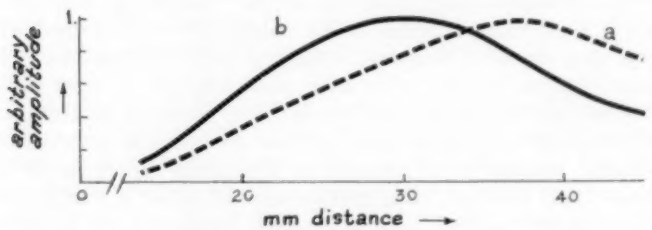

Fig. 10. Envelopes over the second (negative) peaks of the displacement patterns of which Fig. 12 gave two examples. a.—without amplitude limitation; b.—with amplitude limitation of the applied signal.

present phase of the work was reached. These filmed bulges looked very peculiar with their spatial and temporal separation of successive peaks of the bulges.

Fig. 10 shows that after amplitude limitation of the applied signal the envelope over the traveling bulge alters in that the amplitude maximum occurs more proximally along the partition. The latter finding is easily explained. The steeper slopes of the center clipped bulge have shorter time constants. In this manner transient signals of long time constants but of extremely large amplitudes may produce traveling bulges of a shape which is normally associated with signals of shorter time constants; thus the assumption of nonlinear distortion would be able to explain the observation of cochlear injury

after stapes mobilization. This explanation is admittedly not based upon direct evidence; it is offered as a hypothesis which appears to be consistent with other known facts of cochlear mechanics.

After this detail had been brought to a satisfactory solution, the present authors became interested in the more general problem of *acoustic trauma.* The cases presented in the foregoing are all very characteristic of acoustic trauma and, although from that standpoint not presenting anything new, confirm and document once more a familiar pattern: a hearing loss centered around 4,000 cps (the well-known 4,096 cps notch) corresponding to a localized cochlear lesion in the 8-12 mm. region. Such lesions are characteristically produced by acoustic transients (or by their bone-conducted equivalents) of rather high peak intensities. This is in contrast to a so-called noise trauma which results from prolonged and repeated exposure to noise, usually of lesser intensities. The salient point is that whereas a noise trauma is most likely the outcome of a slowly accumulating exhaustion on the cytochemical or enzymatic level without gross tissue destruction, acoustic trauma is the product of a *physical* injury involving local tissue lesions. Admittedly, much of what is finally seen histologically as the result of acoustic trauma is due to tissue degeneration *after* the injury; however, this is irrelevant from the present viewpoint and serves only to illustrate the apparent poor ability toward self-repair of the organ of Corti. In the following an attempt will be made to define the physical causes of acoustic trauma based upon purely mechanical considerations of cochlear stimulation and response.

The present inquiry to be sure is not the first into the problem of acoustic trauma. Two schools of thought appear to exist, specifically with regard to the origin of the 4,096 cps notch considered to be highly characteristic of acoustic trauma: *1.* the *mechanistic* view which holds that for one reason or another strong destructive forces develop in this particular region (*e.g.*, the "Dual-Eddy" Theory of Ruedi and Furrer[11] or the "Jet" Theory of Hilding[7]); *2.* the *locus-minoris-resistentiae* view which maintains that this region is especially vulnerable (*e.g.*, due to insufficient blood supply at the junc-

ture of the cochlear and cochlea-vestibular arteries as suggested by Guild[5]). While not having anything new to offer, neither pro nor con, concerning the second viewpoint, the present authors feel that they have a new concept to present which concerns the possibility of a localized mechanical effect.

A brief comment may be in order concerning the cochlear action of headblows and of surgical manipulations, such as the use of mastoid gouges in the immediate vicinity of the inner-ear capsule. The stimulus is via bone conduction. In cochlear models, in which "bone" conduction can be demonstrated, the hydrodynamic events resulting from "air" and from "bone" conduction are exactly alike.[18] It is recalled that Bekesy,[2] and later Barany,[1] succeeded in mutual cancellation between air- and bone-conducted signals. Their results also serve to demonstrate the identity of these two modes of stimulation as regards their cochlear mechanism.

The stumbling block with respect to the localization of cochlear lesions caused by acoustic trauma lies again (as before in the problem of stapedial manipulations) in the fact that the amplitude in the basal portion is not the maximal amplitude. Fig. 8 presented a typical case with maximal amplitude at a point which is at 40 per cent of the total length of the partition; furthermore, the envelope over the displacement amplitude is rather broad (see Fig. 8) covering practically the entire length of the partition. Third, it is hard to realize why the most basal portion is so conspicuously spared. The question, of course, is whether with regard to the lesions observed the magnitude of the displacement amplitude is the significant factor. It appears not, according to the following simple consideration: If one tries to tear a piece of paper while holding it between both hands and suddenly moving them apart, it is not only important *how far* the hands move (*i.e.*, the amplitude) but also *how fast* such a motion is executed. Expressed more formally, the breaking point of the paper is determined by the *stress* produced during the action described. *Stress* is *force* per *unit area* and *force* is *mass* times *acceleration* (it is in the acceleration that the time factor comes in).

In applying the stress concept to the cochlea it appears that the mass (per unit area) of the tissues involved, *ie.*, of the organ of Corti, does not vary greatly with distance. It is, therefore, safe to state that the stress upon the cochlear partition encountered during its own displacement is in first approximation proportional to its acceleration. From the data available on the transient response of cochlear models it is possible to derive the acceleration pattern, *i.e.*, the stress.

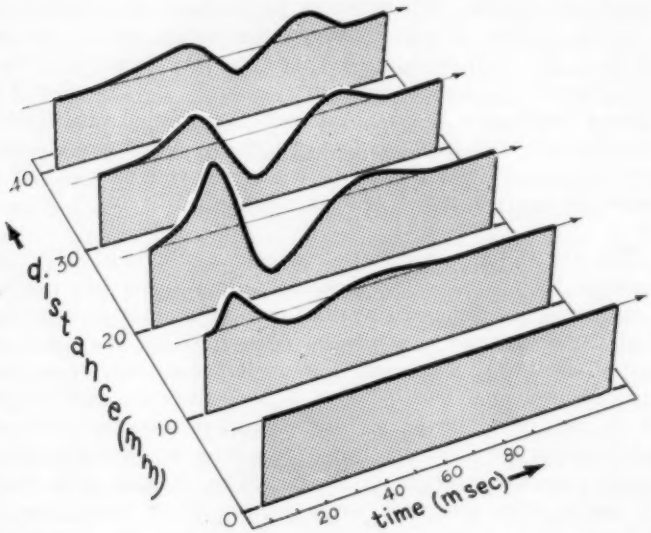

Fig. 11. Displacement pattern with time at various points along the partition; 3-dimensional presentation; x-axis: time, y-axis: amplitude; Z-axis: distance.

Fig. 11 shows once more the traveling bulge, this time presented in a 3-dimensional manner: distance - time - amplitude. Of the series of positive and negative displacements taking place at each point only the first positive peak is of interest here since it involves least time and consequently maximal acceleration. The pertinent time factor, the *rise time* toward the first peak, is plotted *vs.* distance in Fig. 12-a, in a semi-logarithmic manner. The graph indicated that the rise time

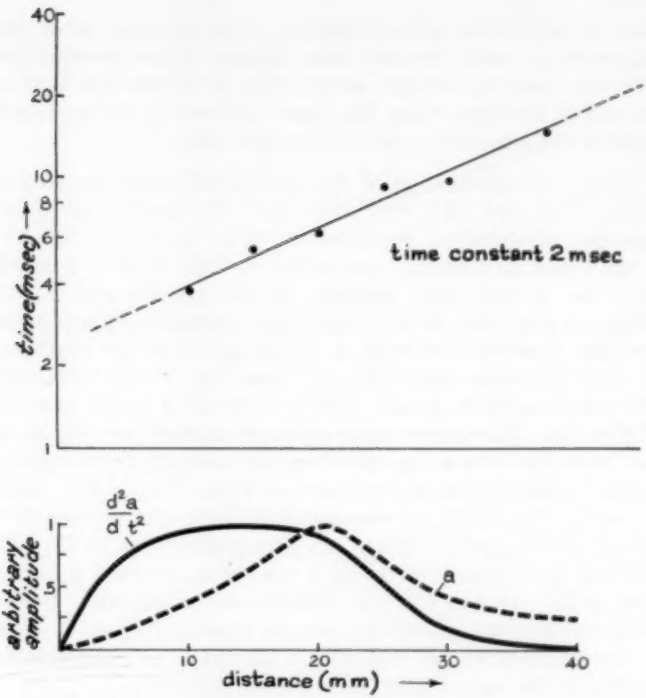

Fig. 12. (above) Rise times of the first positive peaks of Fig. 9 vs. distance. Time is given in a logarithmic manner. (below) Envelope over the displacement amplitude (a) of the first peaks of Fig. 9 and that over the corresponding acceleration pattern (d^2a/dt^2). Note—amplitudes in this and Figs. 11-13 are arbitrarily set to unity.

is shortest at the basal end of the partition, showing an exponential increment thereafter. The ratio between the amplitude at each point (shown once more in Fig. 12-b) and the square of the rise time gives the acceleration pattern along the partition. (A more accurate way of doing this would have consisted in forming the second derivative of the time-displacement pattern of Fig. 11. The difference between both methods is bound to be small.) Fig. 12 indicates that with reference to the envelope over the displacement amplitude the new envelope is shifted toward the direction of the cochlear base. Although the maximum itself is still broad, the decre-

ment of amplitude of acceleration with distance after the maximum is much steeper than before. Since acceleration had been taken to indicate stress, Fig. 12 shows that *most of the stress develops along the basal portion of the partition.* Notably the extreme basal end remains free.

Simple reconsideration of the operational steps involved in graphs 12-a and 12-b will show that the location at which maximal acceleration develops depends upon two factors: *a.* the place of maximal amplitude (which in turn depends upon the inverse time constant of the signal) and *b.* the change in rise time of the bulge with distance. Although the rise time is always shortest at the basal end of the partition, its rate of change again depends upon the inverse time constant of the applied signal. This is illustrated by the example of Fig. 13. The longer time constant makes the change in rise time less steep and produces the amplitude maximum farther distally than in the case of Figs. 11 and 12. Consequently, the shift of the envelope over the acceleration pattern in Fig. 13 is slightly less pronounced than in Fig. 12, although it is again shifted in a proximal direction with respect to the envelope over the displacement amplitude. Unless there is amplitude limitation due to overloading as in Figs. 9 - 10, maximal stress will not in all cases be concentrated exactly in the same region in the basal portion.

One other point deserves comment: It was noted in connection with Fig. 12 that the extreme basal end of the cochlear partition remained free of stress. One might ask: Was that true only for the particular situation depicted or is that a general rule? It would be logical to assume that for very short time constants the location of maximal stress should approach the basal end of the partition. Although this is correct, it turns out that the *sensitivity* of the model to signals with such brief time constants is so low that no sizable displacement amplitude, and thus no appreciable stress, can develop unless it comes to very large signal amplitudes. The low sensitivity of the cochlear partition to signals of brief time constants is a built-in property. Basically, the model represents a series of low-pass filters. Their upper-frequency limits vary from high to low along the partition. These filters

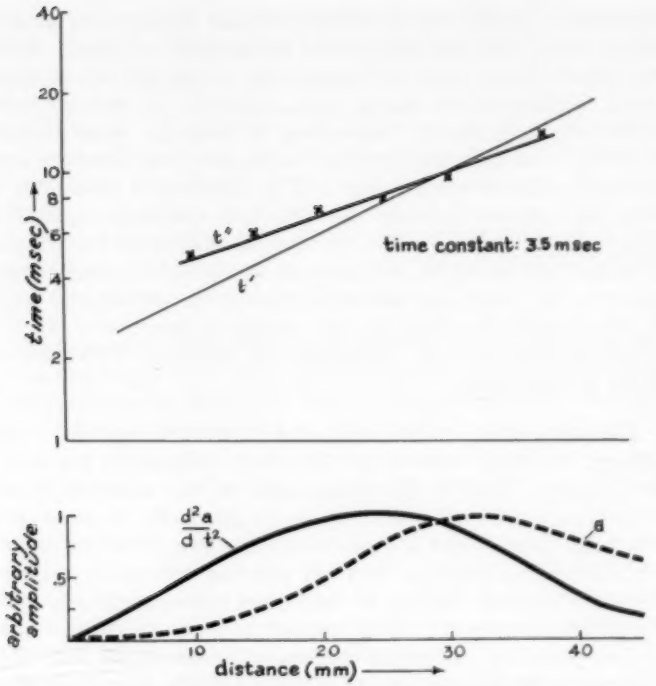

Fig. 13. (above) Rise time (t'') of the first positive peaks vs. distance for a signal with slower time constant. For the sake of comparison the function of Fig. 12-a (t') is included. (below) amplitude (a) and acceleration (d^2a/dt^2) pattern for the same signal.

are not sharply tuned; nonetheless, there is a definite lessening of sensitivity as frequency exceeds a certain value, or what amounts to the same, as time constants become too brief, and optimal stress is a *compromise* between the *de*creasing sensitivity and the *in*crease in rise time of the traveling bulge with inverse time constants of the applied signal. Because of the spatial distribution of frequencies along the cochlear partition *optimal stress must develop some distance from the extreme basal end of the partition.*

The question to be considered next is whether the stress associated with the displacement pattern along the cochlear

partition is really representative of that leading to cochlear injury, *i.e.*, to the loss of hair cells in the organ of Corti. Since the latter results from overstimulation it may be well to state what constitutes the normal stimulation of the sensory cells in the organ of Corti. According to Bekesy's experimental evidence,[4] the ultimate stimulus to the hair cells consists of a bending of their sensory hair. This bending is caused by a *shearing* motion between the tectorial membrane and the organ of Corti proper. Bekesy[4] had distinguished two modes of shear motion which, in response to sinusoidal stimulation, occur in two distinctly different places: *a. radially directed* in the region proximal to the amplitude maximum of the traveling bulge and *b. longitudinally directed*, in the region distal to that point.

Shearing action can be duplicated in cochlear models.[17] An attempt was made to study its pattern in response to transient stimulation. Due to the minuteness of the amplitudes involved, no precise measurements were obtained; however, the following impressions were gained: The two different modes (radial and longitudinal motion) overlap each other widely, the radial motion forming its maximum more proximally than the longitudinal mode. With respect to time, the longitudinal motion precedes the radial motion. The envelopes over the two modes were found not to differ radically from that over the traveling bulge. Rise times at each point are identical to those of the traveling bulge; therefore, the conclusion seems justified that the *stress pattern in the domain of shearing motion* is *very similar to that of Figs. 12 and 13.*

The concept presented here, that acoustic trauma is determined by the distribution of *stress* along the cochlear partition, must also apply to pure tones. Stress was said to be proportional to acceleration. In sinusoidal events, acceleration varies with the square of frequency. This is borne out by experience. It is the consensus of opinion that (in the words of Davis, et al.[6]) "higher frequencies are more effective than low frequencies in producing hearing loss."

Of particular interest from the aspect of exposure to transients is a recent study by Meyer zum Gottesberge.[10] This

author determined the temporary threshold shift resulting from exposure to various bands of broad-spectrum noise. (The relation between this and the present problem is obvious.) Among other facts not relevant to the present problem, Meyer z. G. observed that the frequency at which maximal shift occurred was, as a rule, the upper limiting frequency of the band presented. There was one exception: The frequency of maximal shift never went higher than 4,000 cps, *i.e.*, even for bands consisting of frequencies higher than this limit. Optimal shift was obtained only when the band included 4,000 cps or was near to that frequency.

These results are the more significant as in cochlear models, when the response to noise bands is tested, the amplitude peak invariably occurs *below* the upper frequency limit of the pass band[18]; therefore, Meyer z. G's results when interpreted from the standpoint of the present concept seem to indicate that the most effective stress is always caused by the highest frequency in the band: *e.g.*, the frequency which (in terms of its traveling bulge) has the fastest rise time. The upper limiting frequency of 4,000 cps then represents a *compromise* between the *de*crease in sensitivity toward higher frequencies and the still *in*creasing rise time. The point of highest sensitivity of the human ear is known to be between 2,000 cps and 3,000 cps, *i.e.*, definitely lower than 4,000 cps.

SUMMARY.

It is well known that high energy acoustic signals, such as those created by a blast in air or a blow to the head, can cause cochlear damage having its maximal effect in the upper basal turn. Such lesions can also be created by manipulation of the stapes during the course of surgical procedures. The amplitudes of such maneuvers can be very large and the time constants are long. The resulting cochlear injuries are identical to those resulting from stimuli having short time constants.

Animals with experimentally produced footplate fractures frequently sustain rupture of the saccule, as well as injury to the upper basal and lower middle turns of the cochlea. Sac-

cular rupture also occurred in one of ten animals subjected to head blows. The cause for the saccular injury is not clear.

A new concept is developed concerning the mechanism of acoustic trauma. The assumption is made that the ensuing tissue damage is a function of the physical stress resulting from acoustic stimulation. Experiments on cochlear models using transient signals indicate that the closer the stress is concentrated to the basal end of the cochlea the shorter is the time constant of the applied signal. Since the sensitivity of the model falls off for signals with very short time constants, a region of optimal stress develops close to but not directly at the extreme basal end of the cochlea.

It is possible that signals of relatively long time constants, but of very large amplitudes, produce injurious stresses in the basal region of the cochlea due to nonlinear distortion.

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AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY HOME STUDY COURSES.

The 1960-1961 Home Study Courses in the basic sciences related to opthalmology and otolaryngology, which are offered as a part of the educational program of the American Academy of Ophthalmology and Otolaryngology, will begin on September 1 and continue for a period of 10 months. Detailed information and application forms can be secured from Dr. William L. Benedict, the executive secretary-treasurer of the Academy, 15 Second street S.W., Rochester, Minn. Registrations should be completed before August 15.

HISTOPATHOLOGY OF THE OTOSCLEROTIC FOOTPLATE*

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While a great deal of histopathological study of otosclerosis has been done at the level of macroscopy and light microscopy, for several reasons comparatively little has been contributed by the more advanced techniques of histopathology.

First, the study of undecalcified bone is a difficult one and the technical problems, while not insurmountable have hampered progress in this direction. Second, the only otosclerotic bone available in the past was obtained at autopsy or in recent years during fenestration, in the small percentage of cases where the cupula or an ossicle presented an otosclerotic involvement.

With the advent of the Shea fenestration of the oval window, the footplate of the stapes is removed as entirely as surgically possible, and large amounts of biopsy material have become available in this way.

The authors of this paper have collaborated and pooled their material in an attempt to contribute to the knowledge of histopathology of otosclerosis.

In reviewing the literature on otosclerosis, it is interesting to note how detailed and accurate were the pathological de-

*Read at the meeting of the Middle Section of the American Laryngological, Rhinological and Otological Society, Inc., Chicago, Ill., Jan. 18, 1960.

Editor's Note: This manuscript received in The Laryngoscope Office and accepted for publication April 6, 1960.

scriptions of the 1890-1910 period and how little has been contributed since.

To Valsalva in 1735, is attributed the first gross description of ossification of the annular ligament of the fenestra ovalis as a cause of deafness. Other great anatomists like Morgagni in 1766, and Meckel in 1777, confirmed this observation. Toynbee in 1844 dissected 41 temporal bones and found one case of bilateral ankylosis of the footplate of the stapes. By 1857 Toynbee had studied 1,659 temporal bones and found 92 cases of osseous ankylosis of the stapes to the fenestra ovalis. He called it one of the most common causes of deafness.

In that era, many authors described grossly the pathological picture of otosclerosis, among them Voltolini, Politzer, Lucae, Schwartze and Troeltsch. Moos reported an associated hyperostosis of the petrous bone and the narrowing of the porus acusticus internus.

The first histological study listed in the American Otological Society Resume of Literature on Otosclerosis is by Haberman in 1891. He discussed the sharp characteristics differentiating pathological bone from normal bone, calling attention to the deeper staining with hematoxylin and carmine, the increased size of the marrow spaces, the very irregular construction of the bone, and the dilated vessels. He remarked that the diseased bone looked like calcified cartilage. This description of otosclerosis is still faultless today.

Bezold in 1893 added the description of young osteoid tissue with many cellular marrow spaces and osteoclasts forming eroded lacunae. The normal cartilaginous portion of the footplate was almost entirely replaced by osteoid tissue, and the anterior part was eight to ten times thicker than normal, due to new bone formation.

In 1893 Politzer also concluded from his investigations that the disease originated from the labyrinthine capsule and extended to the stapes, finally leading to ankylosis; he also described round window and labyrinth involvement, and felt that the distinctive staining and the large marrow spaces were the important criteria for diagnosis of otosclerosis.

Hartman in 1898 observed the abnormal shape, size and arrangement of the osteocytes. The fact that they were more numerous in the vicinity of normal bone lead him to believe that otosclerosis consisted of newly developed connective tissue bone.

Siebenmann in 1899 described absorption of bone by osteoclasts with dilatation of the Haversian canals and increased

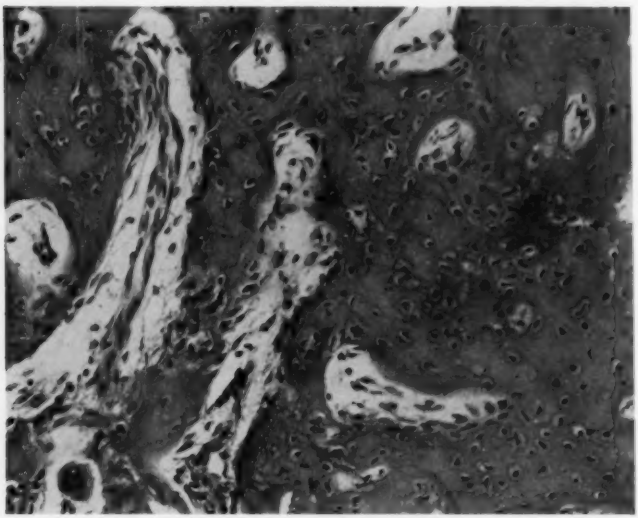

Fig. 1. Otosclerosis Type IV. Large number of osteocytes, misshapen and not oriented. Absence of lamellation. Large, cellular marrow spaces.

connective tissue spaces. The newly formed osteoid zones showed irregularly arranged misshapen bone cells with abnormal extension processes. In addition the interglobular cartilaginous spaces were replaced by newly formed bone.

He wrote that as the disease ages the spongy character disappears, replaced by a lamellar structure with concentric arrangement of bone cells with shrunken nuclei. That which remains spongified proves to be old in its staining, the reaction is then strongly eosinophilic.

In 1900 Manasse described typical Howship's lacunae with osteoclasts and coexistent bone apposition.

Holinger in 1901, studied Siebenmann's specimens of stapes ankylosis with labyrinthine spongification. He observed resorption and new bone formation occurring simultaneously, and replacement of interglobular spaces by newly formed bone; also the cartilage of the footplate was replaced by bone

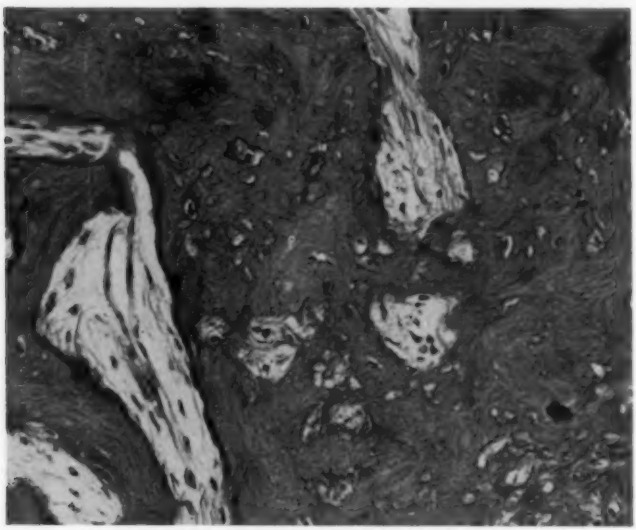

Fig. 2. Otosclerosis Type III. Fewer osteocytes. Nuclei sometimes absent. Absence of lamellation. Marrow spaces less cellular.

in connection with large blood vessels parting from the bone. The spongy spaces were so large that the process could be called a true osteoporotic one, except that there was much new formation of bone. He stated that sclerosis and similar words to indicate this disease are without meaning, pathologically or clinically. "Spongification of the labyrinth is a well defined disease clinically or pathologically."

In 1905 Alexander reported a case of congenital deafness

with partial stapes ankylosis and typical otosclerotic foci in the labyrinthine capsule. He used the term "ground substance" and stated that it was more deeply stained by hematoxylin in otosclerosis than the ground substance of normal bone.

Bruhl in 1905 described the bluish coloration of the bone (blue spongiosa) replacing the annular ligament in a posterior

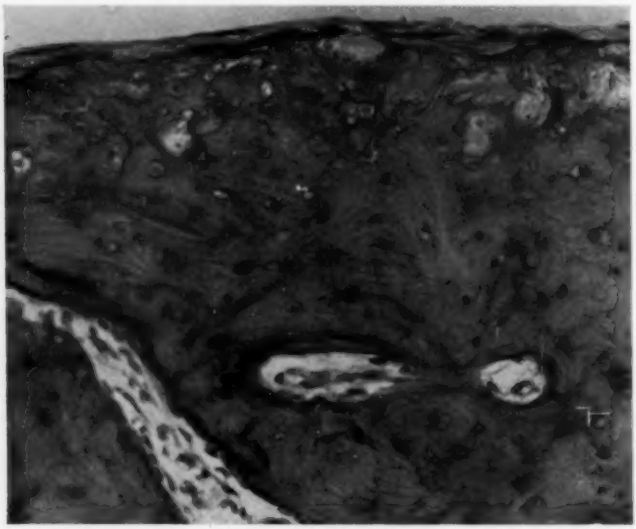

Fig. 3. Otosclerosis Type II. Nuclei often missing. Presence of lacunar canaliculi. Attempt at lamellation. Marrow spaces small, new bone apposition.

process. There the osteocytes were large, misshapen, and numerous, whereas in the more anterior focus staining pink, there was a concentric arrangement of small bone cells. He later said that the combination of active formation of bone by osteoblasts and breaking down by osteoclasts produced an entirely new bone so that the pathological bone always appeared like a foreign body.

In 1906 Schilling added to the usual list of characteristics,

the composition of the marrow substance which shows more nuclei and connective tissue fibers than that of the ordinary spongiosa.

In 1912, Alexander described otosclerotic foci as follows: A very cellular bone rich in calcium, presenting remarkably large cavities which are traversed by numerous pathologically

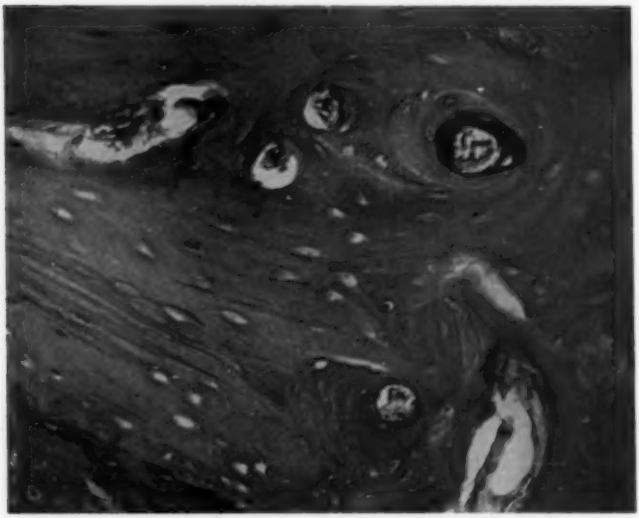

Fig. 4. Otosclerosis Type I. Well oriented osteocytes, nuclei often missing. Regular lamellation. Marrow spaces narrow and inactive.

enlarged blood vessels. Between the bone and the vascular wall is a fairly dense network of connective tissue.

Neuman in 1913 refuted a suggestion of Mayer that otosclerosis is identical with osteitis fibrosa of Recklinghausen. His objections were founded on the absence of pronounced absorption in the sense of rarefaction in otosclerosis, absence of softening, granulating tissue and cysts and on the preservation of the compact character of the labyrinthine capsule in spite of the most radical transformation of its constituents.

In 1914 Komendentanow found many points of similarity between the bony changes characteristic of rachitis and those characteristic of otosclerosis.

Between 1917 and 1921, Wittmack, Mayer, Manasse, Fisher, Lange, and others reported large series of cases with the now familiar description of the pathological changes of otosclerosis,

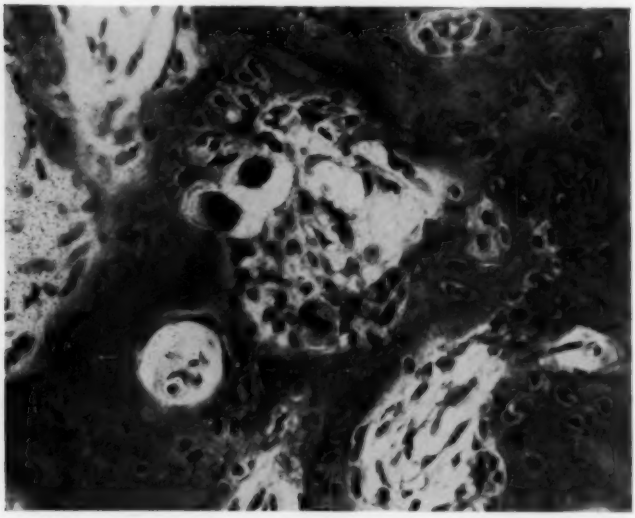

Fig. 5. Two osteoclasts in a Type IV otosclerotic footplate.

the authors arguing only on the significance of some of these changes.

Escat in 1922 describes three phases in the pathology of otosclerosis. The first phase consists of vascularization and return to the osteoid stage. The second phase is that of osteospongiosis with diminution of the size of the capillaries, enlargement of the marrow spaces, appearance of osteoclasts, deep blue staining. The third phase is the rebuilding of a compact osseous tissue, as otosclerosis, with appearance of

osteoblasts, new bone formation along the walls of the marrow spaces and distinctly red staining.

In 1922 Rutin reported a case of otosclerosis associated with fragilitas osseum (osteopsathyrosis) and blue sclera. Although the bone destruction was extensive, to a degree not common in otosclerosis, typical, dense otosclerotic bone was present in the usual site, at the anterior margin of the stapes.

Fig. 6. Type IV otosclerosis showing a marrow space with an osteoclast actively destroying bone, together with new bone apposition on the opposite margin of the space.

In 1923 Jenkins presented two cases of osteitis deformans with deafness and compared his findings with those of otosclerosis. Both diseases showed osteoporosis, but the trabeculae in osteitis deformans were coarser and the bone lamellae more distinct. The limits of osteoporosis were sharply seen in otosclerosis but found only by careful search in osteitis

deformans. Large osteoclasts were more numerous in otosclerosis, as were fibroblasts, but fibrous tissue was a more prominent feature in osteitis deformans. The stapes was not affected in either case of osteitis deformans. In both diseases there was a dense staining of the bone.

Weber, in 1933, wrote an excellent discussion of the blue mantle in otosclerosis. He defined the blue mantle as begin-

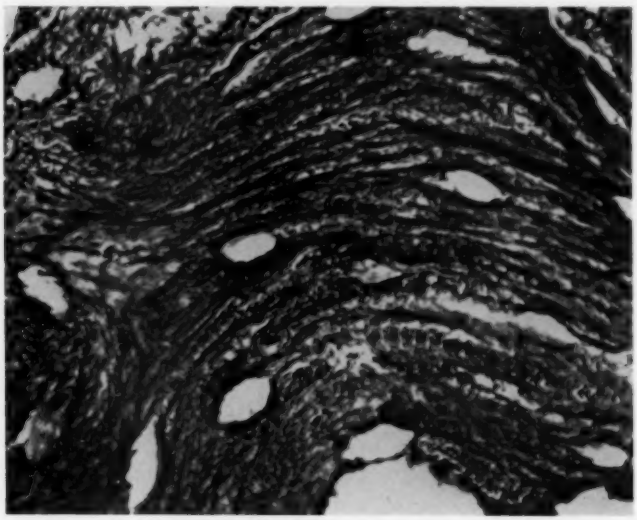

Fig. 7. Appearance of the fibrillar substance in a well lamellated bone. (Silver stain.)

ning as an area of resorption. The cavitation thus formed represents a Howship's lacuna. The blue mantle represents new bone formation after the previous resorption of the vessel space. The new bone formation has a pathological matrix consisting of blue staining cementum and sparse criss-crossed fibrils forming a plexus. He was the first to study otosclerosis under polarized light.

Greifenstein in 1935 showed that after traumatic injuries the marrow tissue of the young otosclerotic focus exhibits a

lively regenerative activity in the sense of normal bone formation.

In the following years one finds far less literature concerned with the descriptive pathology of otosclerosis. The contributors include F. R. Nager in 1938 and 1939, S. R. Guild in 1944, Nylen in 1949. In 1950, S. R. Guild pointed out that

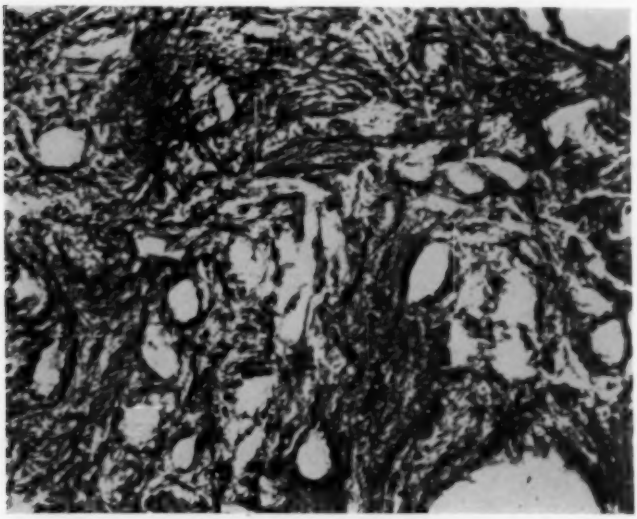

Fig. 8. Disorientation of the fibrillar substance in otosclerosis. (Silver stain.)

nearly 30 per cent of the cases of otosclerosis he studied were unilateral and was concerned with the physiological fact that in any person the blood has supplied both otic capsules with the same nutritional factors, for identical lengths of time. He apparently did not feel that constitutional factors and otosclerosis were in any way related.

Lindsay showed that an attempt to link otosclerosis with other general constitutional factors has so far demonstrated no definite relations either in clinical or in experimental investigations.

Bast felt that otosclerosis could be an attempt to rebuild that part of the otic capsule which was left unstable by late fetal cartilage growth especially in the fissular area.

In 1951 Nager, and Hale in 1952 and 1953 studied specimens taken at surgery from the site of the fenestra novovalis.

In 1952 Brunner introduced the idea that there are preotosclerotic changes, consisting of degeneration of the carti-

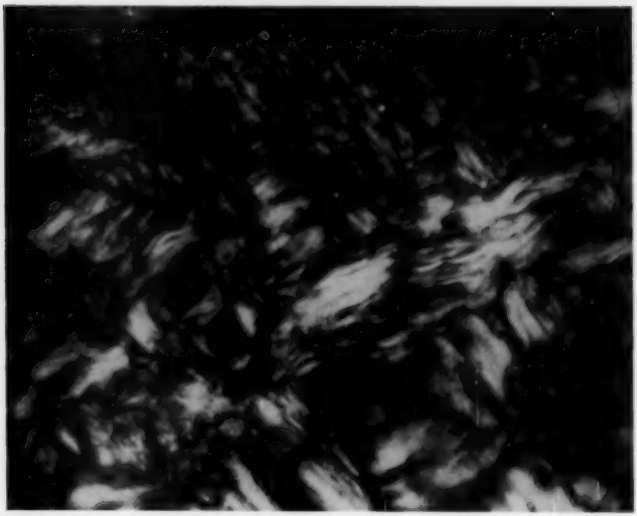

Fig. 9. Braided appearance of otosclerotic bone on polarized light.

lage at the frame of the window and of the appearance of the blue mantles previously described by Manasse. These blue mantles are a broadening of the normal marginal sheaths of the blood vessels. These are called preotosclerotic changes because they are found throughout the labyrinthine capsule in otosclerosis and in some temporal bones with no actual otosclerosis. He felt that they are hereditary and do not produce clinical symptoms by themselves.

In 1953, R. F. Ogilvie and I. S. Hall published a thorough

description of otosclerosis of the fenestration site of 13 per cent of 125 otosclerotic subjects. They remarked that the diffuse damages involve absorption and deposition of the bone through osteoclastic and osteoblastic activity respectively and thereby leads in sequence to an abnormally cancellous, mosaic, and relatively normal architecture of the bone. The immature bone is basophilic, excessively cellular and woven, while the mature bone is acidophilic, normally cellular, and laminated. As for the so called blue mantles they are regarded as a focal manifestation of the diffuse damage.

Bellucci and Wolff in experimental animals created surgical traumas at the oval window, and reported the effects of cautery on the ossicles, and labyrinthine bone. They were interested in the question of healing after stapes mobilization for otosclerosis.

In order to provide a basis for discussion and mutual understanding of the types of otosclerosis involving the footplate, we have attempted a classification based on the degree of activity of the disease. The experience with the first 120 footplates of otosclerotic stapes makes the basis for this report.

The criteria determining this classification are primarily histopathological, but some consideration was given to the gross structural findings. For instance, in a few cases, without the clinical and microscopic observation of annular involvement of the stapes and of the resulting ankylosis, some of the Grade I, stable, almost normal appearing footplates can be very difficult to diagnose as otosclerotic; also, the character of the focus may be such that most of it has to be removed by drill and escapes pathological study. In some instances of diffuse anterior involvement the surgeon must be satisfied with the extraction of the posterior two-thirds of the footplate only. These factors should be kept in mind as such specimens are not typical of the total disease; however, we were impressed with the findings of almost universal involvement of the stapedial footplates.

The evaluation of the typical pathological features of otosclerosis should deal primarily with the cellularity of the

process. The osteocytes are more numerous than in normal bone; also, in normal bone, about 50 per cent of the osteocytes are vital as evidenced by the presence of nuclei. The number of vital cells in active otosclerosis seems to be markedly increased. The cells appear misshapen, disoriented with swollen, or distorted and pyknotic nuclei, and the cytoplasmic processes lying in the canaliculi are absent.

A second feature of evaluation is the increase in marrow spaces. In the normal stapes, the footplate shows few marrow spaces and the crura none, as a rule. In otosclerotic bone, there is an increase in number and activity of the cells of the marrow spaces resulting in resorptive changes forming new spaces as indicated by the presence of osteoclasts. At the same time and sometimes in the same spaces osteoblasts are seen with new bone apposition.

A third most important feature of otosclerosis is the character of the ground or intercellular substance. Intercellular substance consists of two major elements: fibrillar substance and cementum. In otosclerosis, the amount of the basophilic cementum is increased. Otosclerosis is characterized by an immature type of bone, and the immature bone has been described as having a coarse fibrillar substance, but in our slides, thus far, we have not seen it. Our findings indicate that the fibrils are fine, sparse and make patterns in the bone that appear braided or woven. There is often a cementum line between these bundles which appears as a sharp break with silver stain or on polarized light. The total unit volume of fibrillar substance is reduced, not only because of its fineness and sparsity but also because of the increased amount of marrow space and osteocytes.

These histological features and their variations should be kept in mind when one undertakes to grade otosclerosis. One should also note that if it were not for its remarkable and unique location in the temporal bone and for its, as yet, poorly understood relationship with genetics, otosclerosis is difficult to differentiate histopathologically from any other type of immature bone.

We have classified otosclerosis in four main types:

Grade IV is the most active otosclerotic focus of the more immature type. It shows an increased cellularity to a very marked degree in the heavily thickened bone of the footplate, with irregular shape of the osteocytes, swelling of the nuclei, absence of demonstrable canaliculi and of lamellation.

The marrow spaces are increased in size and number and show extensive vascularization. They contain many osteoblasts and some osteoclasts. Frequently in the same space, one may observe appositional surfaces of new bone formation contiguous to a very active process of bone resorption by osteoclasts. The intercellular substance consists mainly of blue staining cementum with sparse braided bundles of fibrils.

There usually is a complete absence of the cartilaginous elements in the footplate, a destruction of the annular ligament and an encroachment beyond the normal confines of the stapedial borders. This process should be termed histopathologically, otospongiosa.

A Grade III type of otosclerosis is often less extensive. The cartilaginous elements of the footplate may have disappeared, and the ligament is totally involved. The process cytologically appears definitely less active; there is some attempt at a more regular arrangement of the osteocytes which are fewer in number. Their nuclei are sometimes shrunken, misshapen, and occasionally absent. The marrow spaces are still large from the previous activity but contain less cells in a loose network, and more active bone apposition is taking place. There is less blue staining cementum and more fibrillar substance in the otosclerotic bone.

Grade II otosclerosis shows patching invasion of the ligament and sparse involvement and calcific changes of the cartilaginous portion of the footplate. The lacunae in a larger percentage than normal show the presence of osteocytic nuclei, but they are pyknotic. In Grade II the marrow spaces are inactive, smaller and less cellular. The woven appearance of the fibrillar substance is fuller and occasionally attempts to organize in a lamellar pattern. The cementum is lessened. The histological findings of invasion of the cartilage and annular ligament further substantiate the pathological diag-

nosis. There is a tendency to the appearance of some cytoplasmic processes in the canaliculi.

Grade I otosclerosis, the most inactive of the four types, shows a slight increase in the number of osteocytes. The nuclei are shrunken. The cytoplasmic processes appear with more regularity. The lamellar arrangement on hematoxylin and eosin stain is quite regular. There are few or no marrow spaces. The cementum is not remarkably increased. Grade I then would be difficult to diagnose at all except for three findings:

1. Calcification of the cartilaginous portion of the footplate.

2. Invasion of the annular ligament.

3. Under polarized light or with silver stain the fibrillar substance appears braided rather than lamellated.

SUMMARY.

From the information obtained from our study of the literature, the dynamic approach of present day bone physiology, and the study of these surgical specimens, we present a description of our present theory of the development and extension of the otosclerotic focus: *I.* The vascular budding invades normal endochondral bone in the advancing or developing process. *II.* The marrow space is then created or enlarged by the action of osteolytic processes carried out primarily by the osteoclasts. *III.* This resorption leaves a Howship's lacuna with exposed fibrillar substance some of which is digested along with the resorbed ground substance. *IV.* The newly formed immature bone rich in cementum and poor in fibrillar substance creates a thickened bluish resting line at right angles to the previous linearity of the invaded bone. The bone filling in the defect is highly osteoblastic at this phase and appositional but immature in type (Type IV). *V.* As this phase becomes exhausted, the bone appositioning becomes more adult, leading to an osteosclerosis (shading down to Grade III, II, and I). *VI.* This process occurs within the same focus, at different phases and at the same time; how-

ever certain "metabolic crises" may activate a whole area into advancing pathology. The perivascular process of bone formation is rich in cementum. *VII.* Items I, II, III, and IV are what Manasse called the blue mantle.

CONCLUSION.

Otosclerosis can be considered as another genetic connective tissue disease wherein the advancing vascular buds lay down sparse abnormal fibrillar substance and excess cementum. In conjunction with this disease of the intercellular substance is the excessive cellular activity of the abnormal bone in its most active phase. Thus far, the questions as to why it is prominent in the temporal bone, why it can remain dormant for so long, and why it shows no variance from other immature bone remains unanswered.

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PLASTIC AND PROSTHETIC REPAIR FOR PATIENTS WITH COMPLETE LOSS OF THE LOWER JAW.*

JOHN B. ERICH, M.D.,†

Rochester, Minn.

Complete loss of the mandible fortunately is an uncommon deformity. The patient with an epithelioma so large that the entire inferior maxilla must be sacrificed practically never is cured, and consequently reconstruction of the lower jaw rarely need be considered in such a case; however, there are certain pathologic conditions that involve total removal of the mandible and that do not affect the patient's span of life; in such instances, plastic repair of the defect is of the utmost importance. The conditions to which I refer are osteomyelitis, radionecrosis, and tumors such as adamantinomas involving the entire lower jaw. Then, too, trauma occasionally accounts for loss of the whole mandible.

Total reconstruction of the inferior maxilla by autogenous bone grafts is completely unsatisfactory from both the esthetic and the functional points of view, because there are no muscle attachments by which the graft can function as a mandible. Even though the ordinary kind of intra-oral prosthesis may be ineffective so far as mastication is concerned, it does restore facial contour in such cases and offers the only satisfactory means of reconstruction. In recent years I have found that an intra-oral prosthesis can be prepared with modifications that make it self-retaining (as much as any full lower denture) and allow for mastication of soft foods, while not neglecting cosmetic objectives (see Fig. 1).

As heretofore, the installation of a prosthesis to replace a lost mandible involves preparation of a skin-lined pocket in the mouth. In all cases in which the bone of the lower jaw

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*Read at the meeting of the Middle Section of the American Laryngological, Rhinological and Otological Society, Inc., Chicago, Ill., Jan. 19, 1960.

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Editor's Note: This manuscript received in The Laryngoscope Office and accepted for publication Feb. 8, 1960.

is completely removed, the soft tissues of the lower half of the face become retracted and distorted by scars. An intra-oral incision made behind the lower lip, chin, and cheeks frees these structures so that they may be returned to a more normal position; however, this procedure leaves a raw cavity in the floor of the mouth. The prosthesis for holding the lower lip and chin forward cannot be inserted into this pocket until the cavity has been lined with a split-thickness skin

Fig. 1. a.—Complete loss of mandible from surgical removal of an adamantinoma. b.—Deformity corrected by combined use of intra-oral prosthetic appliance and clavicular tube flap of skin inserted in floor of the mouth and submental region.

graft. Construction of a stent (mold) to immobilize such a skin graft for a few days while it heals to the walls of the cavity poses a problem, because the mandible is absent, and no lower teeth are present to which the mold can be fixed. To meet this situation, I have prepared a mold in two segments as shown in Fig. 2.

In the construction of the upper segment, softened dental compound contained in a metal tray is employed to obtain an impression of the upper dental arch and palate. When the compound has cooled and hardened, it is removed from the mouth and tray, after which it is reinserted into the oral

cavity to form a sort of splint covering the upper teeth and palate (see Fig. 2).

In preparing the lower segment, a large quantity of softened dental compound is introduced into the surgically prepared pocket back of the lower lip and cheeks. With the upper segment of the mold in proper place over the upper jaw, the patient bites into the softened compound below and holds the

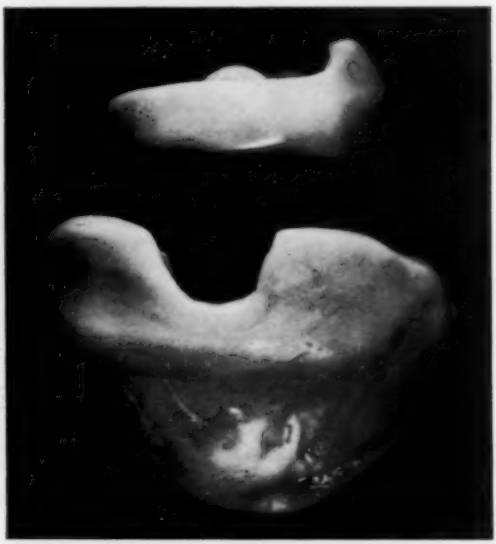

Fig. 2. Mold (stent) made in two segments for immobilizing skin graft in mouth after total loss of mandible. (Skin graft is used to line pocket surgically prepared behind lower lip and chin for reception of prosthetic device.)

maxilla motionless until the lower bulk of compound cools and hardens. After removal of both segments from the mouth, the lower mass of hard compound is trimmed to the desired contour and a through-and-through hole is established anteriorly, into which a catheter or straw can be inserted for feeding the patient (see Fig. 2).

A thin, split-thickness skin graft is wrapped around and

stuck to the outer side of the lower compound segment with mastisol (a solution of mastic in benzene). The two segments of the mold are now introduced into the mouth of the patient. The lower segment is immobilized against the upper segment and against the lower lip and cheeks by means of adhesive tape passed under the chin and up over the head.

The two-piece stent is left undisturbed in the mouth for seven days, during which time the skin graft heals to the

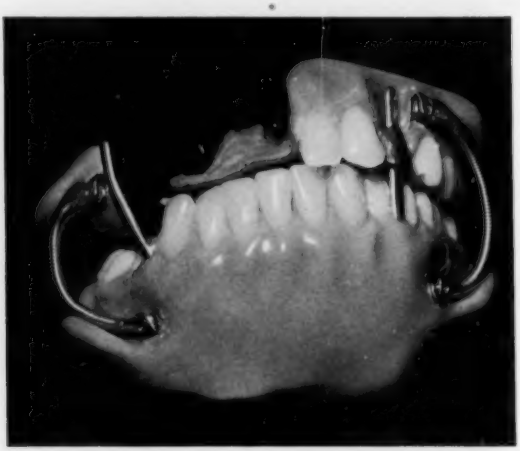

Fig. 3. Intra-oral prosthetic appliance used in total loss of mandible when clavicular tube flap of skin is not used (see text).

walls of the artificially created pocket. Subsequently the mold is reproduced in an acrylic material, thus being made suitable for wearing until a prosthetic appliance can be prepared.

In most cases of this kind I have had a dentist construct this prosthetic appliance as illustrated in Fig. 3. Because there are no means of retaining the appliance in proper position, it would roll around in the mouth like a ball in a socket. To give some stability to the apparatus in the mouth, metal springs from the prosthesis to a partial or full upper denture are necessary; these springs push the device down when the

patient opens his mouth. In addition, a vertical bar on each side of the prosthetic device maintains the lower appliance in correct alignment with the upper denture; these bars slide through metal rings in the upper denture.

Often after such a prosthetic device has been introduced into the mouth, the lower lip is stretched and tense, sometimes to such a degree that the patient is unable to bring the lips into apposition. If such is the case, elastic bands stretched between adhesive tape over the chin and lower lip below and

Fig. 4. Elastic traction on adhesive tape for stretching lower lip and chin up over intra-oral prosthesis (see text).

adhesive tape over the head above will elevate the lower lip until it comes in contact with the upper lip (see Fig. 4). Although this form of elastic traction to the lower lip need be used for only a few days, several months may be required for the muscles of the lower lip to develop sufficiently to impart to the lower lip a completely normal contour.

Even though this type of prosthetic appliance is beneficial in its restoration of normal facial contour, it is unsatisfactory from a functional standpoint. Usually patients find it necessary to remove such a device at mealtime because they are unable to manipulate it properly during the swallowing of liquid food.

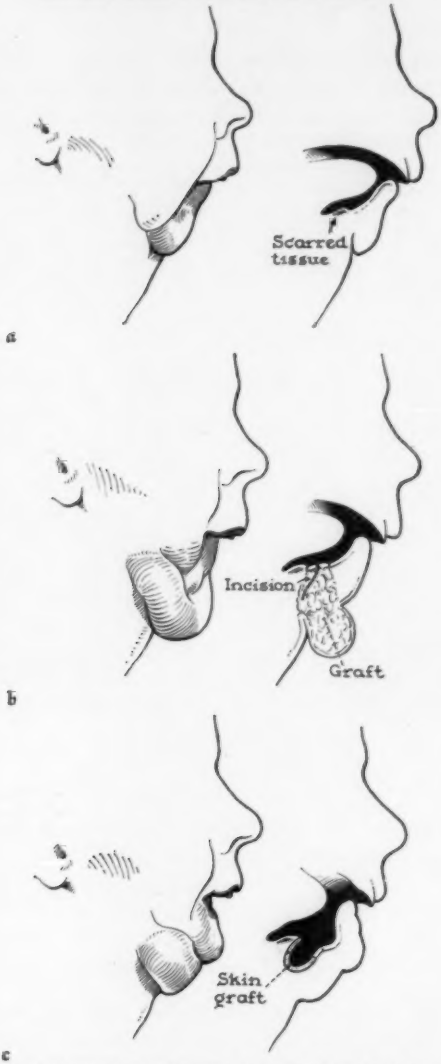

Fig. 5. Use of clavicular tube flap in loss of mandible. a.—Retraction of lower lip and chin. b.—Clavicular tube flap has been wedged in between the lower lip and chin and the floor of mouth. All fat in tube is left intact. Dashed line indicates where intra-oral incision is made down into tube flap. c.—When edges of incision are separated, resulting large pocket must be lined with split-thickness skin graft. Pocket receives extension added to prosthesis to aid retention of appliance.

In recent years I have learned that the prosthetic device is retained in the mouth much more effectively if a tube flap of skin elevated along one clavicle is inlaid in a horizontal direction between the chin and floor of the mouth (see Fig. 5). The introduction of this mass of soft tissue lessens or eliminates the backward pull of scar tissue on the lower lip; otherwise, the lip often is so tight over an intra-oral prosthetic appliance that it tends to force the apparatus out of the mouth. Moreover, the prosthesis can be extended into the inlaid tube flap, which provides considerable stabilization for the appliance (see Fig. 5-c). As a matter of fact, in an oral

Fig. 6. (Loss of mandible due to radiation necrosis.) Front and side views of clavicular tube flap of skin elevated for use in providing soft tissue for scarred floor of mouth.

receptacle constructed thus, the prosthetic device requires no attachments to the upper denture for retention and can be used to masticate soft foods.

In preparation of the tubed skin graft, a double pedicle flap of skin is elevated and tubed in an oblique direction across one clavicle (see Fig. 6). After one month the supraclavicular end of the tube is detached and transferred to one or the other of the submaxillary regions. Three weeks later the infra-clavicular end of the tube is cut off and transplanted to the opposite submaxillary region (see Fig. 7). After another three weeks, a through-and-through incision is made in the submental region into the floor of the mouth, thus completely freeing the chin and lower lip from the floor of the mouth.

The tube flap then can be wedged into this incision to force the lower lip and chin forward.

Horizontal incisions along the anterior and posterior surfaces of the tube divide it into an upper intra-oral portion and a lower external part. The cut edges of the skin on the upper half of the tube are sutured to the oral mucous membrane, and the cut edges on the lower part of the tube are stitched to the adjacent skin margins. By this arrangement the skin on the upper surface of the tube flap forms the epithelial

Fig. 7. (Same patient as in Fig. 6.) Clavicular tube flap of skin attached to either side of chin.

lining of the mouth between the lower lip and the floor of the mouth, and the skin on the undersurface of the tube becomes a part of the external skin covering the submental region. No fat in the tube is disturbed or removed, so a bulk of soft tissue remains behind the chin to hold it forward and prevent subsequent contractures.

After the tube flap is completely healed in its new position, an incision is made through the intra-oral part of the tube flap (see Fig. 5-b). This incision is carried down into the underlying fat of the tube and backward under the tissues of the floor of the mouth. When the incision is spread apart, a rather large pocket is produced for the reception of an ex-

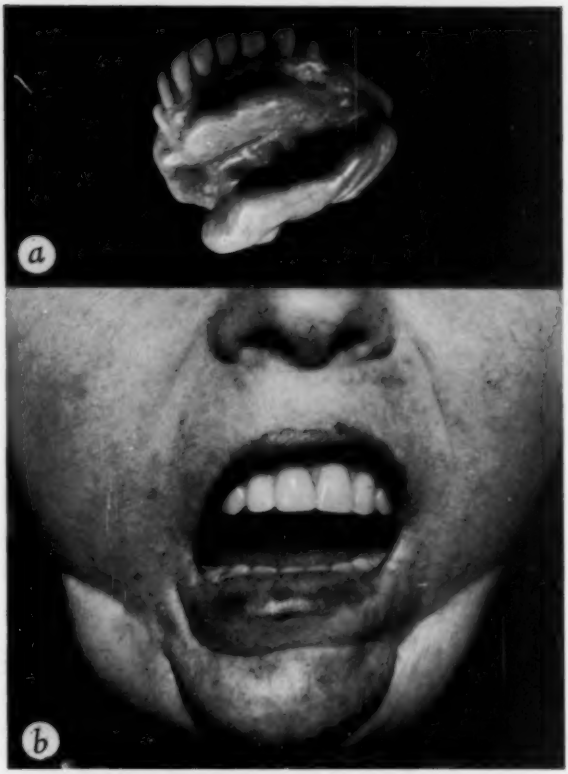

Fig. 8. (Same patient as in Fig. 6.) a.—Prosthesis employed to hold lower lip and chin forward. (Downward extension on this prosthesis fits into skin-lined pocket illustrated in Fig. 5-c.) b.—Prosthetic appliance shown in Fig. 8-a fits almost as well as any full lower denture without the use of springs. By using the muscles of expression about the mouth, the patient can open her mouth and can masticate very soft food.

tension on the proposed prosthetic device. To prevent obliteration of the pocket by scar tissue, it is essential that the cavity be lined with a split-thickness skin graft (see Fig. 5-c).

An acrylic prosthetic device with lower artificial teeth to occlude with the patient's upper teeth or denture is prepared by a dentist; this appliance is made to fit over the tissues in the floor of the mouth and has an extension down into the skin-lined pocket in the inlaid tube flap (see Fig. 8-a).

In the three cases in which I have used this technique, I have found that the prosthetic appliance can be seated securely and that it fits almost as well as does the ordinary full lower denture (see Fig. 8-b). The tube flap of skin eliminates extensive scarring behind the lower lip and chin and leaves

Fig. 9. (Same patient as in Fig. 6.) Postoperative result.

the lower lip and chin nicely contoured (see Fig. 9) and freely movable with no tendency to displace the dental appliance. The patient can learn to masticate soft food by use of the muscles of expression about the mouth, and because the appliance is self-retaining, the patient can also learn to talk satisfactorily.

PROGRAM FOR AMERICAN MEDICAL ASSOCIATION SECTION ON LARYNGOLOGY, OTOLOGY AND RHINOLOGY, 109th ANNUAL MEETING.

June 15-17, 1960, Miami Beach, Fla.

Wednesday, June 15, 1960.

Joint Session of the Section on Laryngology, Otology and Rhinology, Section on the Diseases of the Chest, and Section on Radiology.

1. Panel Discussion on Tumors of the Trachea and Bronchi.

   Moderator: Dr. Paul H. Holinger, Chicago 11, Ill.

   Endoscopist: Dr. Herbert W. Schmidt, Rochester, Minn.

   Radiologists: Dr. Barton R. Young, Philadelphia, Pa.; Dr. Wendell G. Scott, St. Louis, Mo.

   Surgeons: Dr. Robert J. Jensik, Chicago 4, Ill.; Dr. Robert W. Jamplis, Palo Alto, Calif.

2. Panel on Disseminated Diseases of the Chest.

   Moderator: Dr. Harold O. Peterson, Minneapolis, Minn.

   Internist: Dr. James A. Wier, Denver, Colo.

   Chest Physician: Dr. David Radner, Chicago, Ill.

   Endoscopist: Dr. Walter H. Maloney, Cleveland 6, O.

   Radiologists: Dr. Eugene F. Van Epps, Iowa City, Ia.; Dr. Clyde A. Stevenson, Spokane, Wash.

   Surgeons: Dr. Donald L. Paulson, Dallas, Tex.; Dr. William Tuttle, Detroit, Mich.

Thursday, June 16, 1960.

Audiology: Its Progress and Problems.

Kenneth O. Johnson, Ph.D., Executive Secretary, American Speech and Hearing Association, Washington 6, D. C., (By Invitation).

External Otitis: Specific Therapy Based on Accurate Diagnosis.

Edley H. Jones, Vicksburg, Miss.

Address of Guest of Honor.

Louis H. Clerf, St. Petersburg 2, Fla.

Nasal Tip Surgery.

Sam H. Sanders, Memphis 4, Tenn.

Address of Section Chairman.

Paul H. Holinger, Chicago 11, Ill.

Problems and Complications in Head and Neck Surgery.

George A. Sisson, Syracuse 10, N.Y., and Norman E. Johnson.

The Long-Term Care of the Laryngectomized Patient.

George F. Reed, Massachusetts Eye and Ear Infirmary, Boston, Mass.

Friday, June 17, 1960.

Cystadenoma of the Parotid and of the Larynx.

Arthur J. Kuhn, Hammond, Ind.

Effect of Premarin on the Ground Substance.

Maurice Schiff, Capt. (MC) USN, U. S. Naval Hospital, Oak Knoll, Calif.

Cervico-Facial Congenital Anomalies.

Richard T. Farrior, Farrior Clinic, Tampa 6, Fla.

Incidence of Hearing Impairment in a Medical Center Population.

Edmund P. Fowler, Jr., M.D., and Thomas H. Fay, Ph.D., New York 32, N. Y.

Otometric Operations.

George D. Albers, Grand Rapids 3, Mich.

Five Year Results of Stapes Mobilization and Current Results with Vein Plug Stapedeoplasty.

C. M. Kos, University Hospitals, Iowa City, Ia.

Fenestration of the Oval Window.

John J. Shea, Jr., Memphis 4, Tenn.

Use of Ear Canal Skin in Myringoplasty.

William F. House, Los Angeles 57, Calif.

Problems with Tympanoplasty.

Edward C. Brandow, Jr., Albany 10, N. Y.

LADY EWING MEMORIAL.

"The death of Lady Ewing of Manchester, England, in July, 1959, ended a life of devoted service to the cause of the education of deaf children. The world-wide reputation of the Department of Education of the Deaf at Manchester University came about mainly through her own genius as a teacher and her skill in imparting her knowledge to others. From its opening in 1919 until her retirement in 1949, she inspired successive groups of students with her own enthusiasm and conveyed to them something of her steadfast adherence to the principles which she showed were sound.

"It was perhaps fitting that, as she had started, so her life's work ended. From 1912 to 1919 she demonstrated what could be done with young deaf children at the Royal Residential Schools for the Deaf in Manchester, and her closing years were spent in proclaiming the need for the earliest possible training of young deaf children and in giving help to these who were willing to undertake this work.

"Her work won world-wide renown and her advice and help were eagerly sought not only throughout the United Kingdom, but in the Commonwealth and elsewhere as well. Recognition of her work came with honorary degrees and other distinctions. Her friends and former students now feel that this recognition should take a more permanent form and that some suitable memorial to her life and work should be established. They believe that many people, especially those whom she helped directly and indirectly, would be glad to contribute to the cost of its foundation. It has accordingly been decided to establish a Research Scholarship to be known as the Irene Ewing Research Scholarship.

"It is believed that such a Research Scholarship would most fittingly preserve the memory of one who, in our generation, probably did more in her lifetime than any other single person to advance the cause of the education of deaf children."

Upon receipt of the above information from England, a group of Lady Ewing's friends in America felt that they

would like to share in the establishment of this memorial. We would like to offer others in the United States and Canada the opportunity of honoring one who has contributed so much to the education of deaf children throughout the world.

Contributions from the United States and Canada may be mailed to Clarke School for the Deaf, Northampton, Mass. Attention: Miss Numbers.

Checks should be made payable to: Lady Ewing Memorial Fund.

THE MOUNT SINAI HOSPITAL.

An intensive Postgraduate Course in Rhinoplasty, Reconstructive Surgery of the Nasal Septum and Otoplasty will be given July 16, 1960, through July 29, 1960, by Dr. Irving B. Goldman and staff at the Mount Sinai Hospital in affiliation with Columbia University.

Candidates for the course should apply to Registrar for Postgraduate Medical Instruction, The Mount Sinai Hospital, 5th Avenue and 100th Street, New York 29, N. Y.

DIRECTORY OF OTOLARYNGOLOGIC SOCIETIES.

(Secretaries of the various societies are requested to keep this information up to date).

AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. Erling W. Hansen, 90 So. Ninth St., Minneapolis, Minn.
Executive Secretary: Dr. William L. Benedict, Mayo Clinic, Rochester, Minn.
Meeting: Palmer House, Chicago, Ill., October, 1960.

AMERICAN ASSOCIATION FOR CLEFT PALATE REHABILITATION.

President: Dr. J. J. Longacre, 1503 Carew Tower, Cincinnati, O.
President-Elect: Dr. D. C. Samuel Pruzansky, D.D.S., 840 So. Wood St., Chicago, Ill.
Secretary-Treasurer: Dr. Spriestersbach, Ph.D., Department of Otolaryngology, University Hospital, Iowa City, Ia.
Meeting:

AMERICAN BOARD OF OTOLARYNGOLOGY.

President: Dr. Gordon D. Hoople, 1100 E. Genesee Dr., Syracuse 10, N. Y.
Secretary: Dr. Dean M. Lierle, University Hospital, Iowa City, Ia.
Meeting: Palmer House, Chicago, Ill., October, 1960.

AMERICAN BRONCHO-ESOPHAGOLOGICAL ASSOCIATION.

President:
Vice-President: Dr. Daniel C. Baker, Jr., 903 Park Ave., New York, N. Y.
Secretary: Dr. F. Johnson Putney, 1712 Locust St., Philadelphia 3, Pa.
Treasurer: Dr. Charles M. Norris, 3401 Broad St., Philadelphia, Pa.
Meeting: Lake Placid Club, Essex Co., N. Y., May 20, 1961.

AMERICAN LARYNGOLOGICAL ASSOCIATION.

President: Dr. Edwin N. Broyles, Baltimore, Md.
Secretary: Dr. Lyman G. Richards, Wellesley Hills, Mass.
Treasurer: Dr. Francis E. LeJeune, New Orleans, La.
Editor, Historian, and Librarian: Dr. Edwin N. Broyles, Baltimore, Md.
Meeting: Lake Placid Club, Essex Co., N. Y., May ....., 1961.

AMERICAN LARYNGOLOGICAL, RHINOLOGICAL AND OTOLOGICAL SOCIETY, INC.

President: Dr. Fletcher D. Woodward, 400 Locust Ave., Charlottesville, Va.
President-Elect: Dr. John R. Lindsay, Chicago, Ill.
Secretary: Dr. C. Stewart Nash, 700 Medical Arts Bldg., Rochester 7, N. Y.
Treasurer: Dr. K. M. Day, 121 University Pl., Pittsburgh, Pa.
Annual Meeting: Lake Placid Club, Essex Co., N. Y., May 23-24-25, 1961.

AMERICAN MEDICAL ASSOCIATION, SECTION ON LARYNGOLOGY, OTOLOGY AND RHINOLOGY.

Chairman: Dr. Paul H. Holinger, Chicago, Ill.
Vice-Chairman: Dr. Lawrence R. Boies, Minneapolis, Minn.
Secretary: Dr. Walter E. Heck, San Francisco, Calif.
Representative to Scientific Exhibit: Dr. Walter H. Maloney, Cleveland, Ohio.
Section Delegate: Dr. Gordon F. Harkness, Davenport, Ia.
Alternate Delegate: Dr. Dean M. Lierle, Iowa City, Ia.
Meeting: Miami Beach, Fla., June 13-17, 1960.

AMERICAN OTOLOGICAL SOCIETY, INC.

President: Dr. Henry L. Williams, Rochester, Minn.
Vice-President: Dr. Lawrence R. Boies.
Secretary-Treasurer: Dr. James A. Moore, New York City, N. Y.

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Vice-President: Dr. Kenneth Hinderer, 402 Medical Arts Bldg., Pittsburgh, Pa.
Secretary: Dr. Louis Joel Feit, 66 Park Ave., New York 16, N. Y.
Treasurer: Dr. Arnold L. Caron, 36 Pleasant St., Worcester, Mass.

AMERICAN RHINOLOGIC SOCIETY.

President: Dr. Roland M. Loring, 25 E. Washington St., Chicago, Ill.
Secretary: Dr. Robert M. Hansen, 1735 N. Wheeler Ave., Portland 17, Ore.
Annual Clinical Session: Chicago, Ill. (Definite time and place to be announced later).
Annual Meeting: October 1, 1960, Belmont Hotel, Chicago, Ill.

AMERICAN SOCIETY FOR HEAD AND NECK SURGERY.

President: Dr. John J. Conley, New York, N. Y.
Vice-President: Dr. Joseph H. Ogura, St. Louis, Mo.
Treasurer: Dr. F. Johnson Putney, Philadelphia, Pa.
Secretary: Dr. George A. Sisson, Syracuse, N. Y.
Annual Meeting: Palmer House, Chicago, Ill., October 1, 1960.

AMERICAN SOCIETY OF FACIAL PLASTIC SURGERY.

President: Dr. Oscar J. Becker, Chicago, Ill.
Vice-President: Dr. Sam H. Sanders, Memphis, Tenn.
Treasurer: Dr. Joseph C. Miceli, Brooklyn, N. Y.
Secretary: Dr. Samuel M. Bloom, 123 E. 83rd St., New York 28, N. Y.
Meeting: Chicago, Ill., October, 1960.

AMERICAN SOCIETY OF OPHTHALMOLOGIC AND OTOLARYNGOLOGIC ALLERGY.

President: Dr. Walter E. Owen, Peoria, Ill.
President-Elect: Dr. Leland H. Prewitt, Ottumwa, Ia.
Vice-President: Dr. D. A. Skinner, Newark, O.
Secretary-Treasurer: Dr. Daniel S. DeStio, 121 S. Highland Ave., Pittsburgh 6, Pa.
Annual Meeting: Palmer House, Chicago, Ill., October 8, 1960.

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Editors for the Archives of the Society: Dr. Antonio de Almeida, Dr. Gabriel Pôrto, and Dr. Roberto Franco do Amaral.

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Vice-Presidente: Dr. Luis Suñe Medan.
Secretario: Dr. Jorge Perelló, 319 Provenza, Barcelona.
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Vocal: Dr. J. M. Ferrando.

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Chairman: Dr. Walter E. Loch, 1039 No. Calvert St., Baltimore, Md.
Secretary-Treasurer: Dr. Theodore A. Schwartz.

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Presidente: Dr. K. Segre.
Vice-Presidente: Dr. A. P. Belou.
Secretario: Dr. S. A. Aranz.
Pro-Secretario: Dr. J. M. Tato.
Tesorero: Dr. F. Games.
Pro-Tesorero: Dr. J. A. Bello.

CANADIAN OTOLARYNGOLOGICAL SOCIETY SOCIETE CANADIENNE D'OTOLARYNGOLOGIE.

President: Dr. Gordon H. Francis, 925 W. Georgia St., Vancouver, B. C.
Secretary: Dr. Donald M. MacRae, 324 Spring Garden Road, Halifax, Nova Scotia.
Meeting: Jasper Park Lodge, Jasper National Park, Alberta, June 10-12, 1960.

CENTRAL ILLINOIS SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. G. E. Hartenbower, 203 N. Main St., Bloomington, Ill.
President-Elect: Dr. Edgar T. Blair, Springfield, Ill.
Vice-President: Dr. G. LeRoy Porter, Urbana, Ill.
Delegate at Large: Dr. S. G. Baldwin, Danville, Ill.
Secretary-Treasurer: Dr. C. L. Pannabecker, Peoria, Ill.

CHICAGO LARYNGOLOGICAL AND OTOLOGICAL SOCIETY.

President: Dr. George Woodruff, Woodruff Clinic, Joliet, Ill.
Vice-President: Dr. Linden Wallner, 122 So. Michigan, Chicago, Ill.
Secretary-Treasurer: Dr. Robert Lewy, 25 East Washington St., Chicago 2, Ill.
Meeting: First Monday of each month, October through May.

CHILEAN SOCIETY OF OTOLARYNGOLOGY.

President: Dr. Enrique Grünwald S.
Vice-President: Dr. Agustin Estartus.
Secretary: Dr. Marcos Chaimovich S.
Treasurer: Dr. Benjamin Kapkan K.
Director: Dr. Alberto Basterrica A.

COLORADO OTOLARYNGOLOGY SOCIETY.

President: Dr. James T. Blair, Denver, Colo.
Vice-President: Dr. James Rigg, Grand Junction, Colo.
Secretary: Dr. Will P. Pirkey, Denver, Colo.

COLUMBUS, OHIO, OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY.

President: Dr. John E. Arthur.
Secretary: Dr. M. L. Battles.
Meetings: First Monday of October through May, University Club, Columbus, O.

DALLAS ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. Edward A. Newell.
Vice-President: Dr. Thomas M. McCrory.
Secretary-Treasurer: Dr. James L. Baldwin, 1627 Medical Arts Bldg., Dallas, Tex.

FEDERACION ARGENTINA, DE SOCIEDADES DE OTORRINOLARINGOLOGIA.

Secretary of the Interior: Prof. Dr. Atilio Viale del Carril.
Secretary of the Exterior: Dr. Aldo G. Remorino.
Secretary Treasury: Prof. Dr. Antonio Carrascosa.
Pro-Secretary of the Interior: Prof. Dr. Carlos P. Mercandino.
Pro-Secretary of the Exterior: Prof. Dr. James A. del Sel.
Pro-Secretary of the Treasury: Dr. Jorge Zubizarreta.

FIRST CENTRAL AMERICAN CONGRESS OF OTORHINOLARYNGOLOGY.

President: Dr. Victor M. Noubleau, San Salvador.
Secretary-Treasurer: Dr. Hector R. Silva, Calle Arce No. 84, San Salvador, El Salvador, Central America.

FLORIDA SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. G. Dekle Taylor, Jacksonville, Fla.
President-Elect: Dr. Kenneth S. Whitmer, Miami, Fla.
First Vice-President: Dr. William H. Anderson, Jr., Ocala, Fla.
Second Vice-President: Dr. Marion W. Hester, Lakeland, Fla.
Secretary-Treasurer: Dr. Joseph W. Taylor, Jr., 1 Davis Blvd., Tampa 6, Fla.

FOURTH LATIN-AMERICAN CONGRESS OF OTORINOLARINGOLOGIA.

President: Dr. Dario.
Secretary:
Meeting:

FORT WORTH EYE, EAR, NOSE AND THROAT SOCIETY.

President: Dr. Van D. Rathgeber.
Vice-President: Dr. William Skokan.
Secretary-Treasurer: Dr. Paul Rockwell.

GREATER MIAMI EYE, EAR, NOSE AND THROAT SOCIETY.

President: Dr. Mariano C. Caballero.
Vice-President: Dr. Joseph Freeman.
Secretary-Treasurer: Dr. H. Carlton Howard.
Meeting: Quarterly in March, May, October and December on the second Thursday of the month, 6:30 P.M., at the McAllister Hotel, Miami, Fla.

INTERNATIONAL BRONCHOESOPHAGOLOGICAL SOCIETY.

President: Dr. Jo Ono, Tokyo, Japan.
Secretary: Dr. Chevalier L. Jackson, 3401 N. Broad St., Philadelphia 40, Pa., U. S. A.
Meeting:

KANSAS CITY SOCIETY OF OTOLARYNGOLOGY AND OPHTHALMOLOGY.

President: Dr. Clarence H. Steele.
President-Elect: Dr. Dick H. Underwood.
Secretary: Dr. James T. Robison, 4620 J. C. Nichols Parkway, Kansas City, Mo.
Meeting: Third Thursday of November, January, February and April.

LOS ANGELES SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. Max E. Pohlman.
Secretary-Treasurer: Dr. Wendell C. Irvine.
Chairman of Ophthalmology Section: Dr. Carroll A. McCoy.
Secretary of Ophthalmology Section: Dr. Philip D. Shanedling.
Chairman of Otolaryngology Section: Dr. Robert W. Godwin.
Secretary of Otolaryngology Section: Dr. Francis O'N. Morris.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd., Los Angeles, Calif.
Time: 6:30 P.M. last Monday of each month from September to June, inclusive—Otolaryngology Section. 6:30, first Thursday of each month from September to June, inclusive—Ophthalmology Section.

LOUISIANA-MISSISSIPPI OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY.

President: Dr. Lucian W. Alexander, 921 Canal St., New Orleans, La.
Secretary: Dr. Edley H. Jones, 1301 Washington St., Vicksburg, Miss.
Meeting: Edgewater Gulf Hotel, Edgewater Park, Miss., April 8-9, 1960.

MEMPHIS SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

Chairman: Members serve as chairman in alphabetical order monthly.
Secretary-Treasurer: Dr. Roland H. Myers, 1720 Exchange Bldg., Memphis, Tenn.
Assistant Secretary-Treasurer: Dr. William F. Murrah, Jr., Exchange Bldg., Memphis, Tenn.
Meeting: Second Tuesday in each month at 8:00 P.M. at Memphis Eye, Nose and Throat Hospital.

MEXICAN ASSOCIATION OF PLASTIC SURGEONS.

President: Dr. Cesar LaBoide, Mexico, D. F.
Vice-President: Dr. M. Gonzales Ulloa, Mexico, D. F.
Secretary: Dr. Juan De Dios Peza, Mexico, D. F.

MEXICAN SOCIETY OF OTOLARYNGOLOGY.

President: Dr. Rafael Giorgana.
Secretary: Dr. Carlos Valenzuela, Petrarca 332-1, Mexico 5, D. F.

MISSISSIPPI VALLEY MEDICAL SOCIETY.

President: Dr. Arthur S. Bristow, Princeton, Mo.
Secretary-Treasurer: Dr. Harold Swanberg, Quincy, Ill.
Assistant Secretary-Treasurer: Dr. Jacob E. Reisch, Springfield, Ill.

NETHERLANDS SOCIETY OF OTO-RHINO-LARYNGOLOGY. (Nederlandsche Keel-Neus-Oorheelkundige Vereeniging.)

President: Dr. H. Navis, Sonsbeekweg 6, Arnhem.
Secretary: Dr. W. H. Struben, J. J. Viottastraat 1, Amsterdam.
Treasurer: Mrs. F. Velleman-Pinto, Jac. Ohrechtstr. 66, Amsterdam.

NORTH CAROLINA EYE, EAR, NOSE AND THROAT SOCIETY.

President: Dr. J. C. Peele, Kinston Clinic, Kinston, N. C.
Vice-President: Dr. George E. Bradord, Winston-Salem, N. C.
Secretary-Treasurer: Dr. J. D. Stratton, 1012 Kings Drive, Charlotte 7, N. C.
Meeting:

NORTH OF ENGLAND OTOLARYNGOLOGICAL SOCIETY.

President: Mr. G. L. Thompson, 16 Ramshill Road, Scarborough, Yorkshire.
Vice-President: Mr. J. H. Otty, Frizley Old Hall, Frizinghall Road, Bradford, Yorkshire.
Secretary and Treasurer: Mr. R. Thomas, 27 High Petergate, York, Yorkshire.

OREGON ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. David D. DeWeese, 1216 S. W. Yamhill St., Portland 5, Ore.
Secretary-Treasurer: Dr. Paul B. Myers, 223 Medical Dental Bldg., Portland 5, Ore.
Meeting: Fourth Tuesday of each month from September through May, Henry Thiele Restaurant, 23rd and W. Burnside, Portland, Ore.

OTOSCLEROSIS STUDY GROUP.

President: Dr. E. H. Campbell, 133 So. 36th St., Philadelphia 4, Pa.
Secretary-Treasurer: Dr. Raymond Jordan, 121 University Place, Pittsburgh, Pa.
Meeting: Palmer House, Chicago, Ill., October, 1960.

PACIFIC COAST OTO-OPHTHALMOLOGICAL SOCIETY.

President: Dr. John F. Tolan, 1118-9th Ave., Seattle 5, Wash.
Secretary-Treasurer: Dr. Homer E. Smith, 686 Twelfth Ave., Salt Lake City, Utah.
Meeting: St. Francis Hotel, San Francisco, Calif., May 22-26, 1960.

PAN AMERICAN ASSOCIATION OF OTO-RHINO-LARYNGOLOGY AND BRONCHO-ESOPHAGOLOGY.

President: Dr. Paul Holinger, 700 No. Michigan Blvd., Chicago, Ill.
Executive Secretary: Dr. Chevalier L. Jackson, 3401 No. Broad St., Philadelphia 40, Pa., U. S. A.
Meeting: Seventh Pan American Congress of Oto-Rhino-Laryngology and Broncho-Esophagology.
Time and Place:

PHILADELPHIA LARYNGOLOGICAL SOCIETY.

President: Dr. John J. O'Keefe.
Vice-President: Dr. Joseph P. Atkins.
Secretary: Dr. William A. Leil.
Executive Committee: Dr. Harry P. Schenck, Dr. Benjamin H. Shuster, Dr. William A. Leil, Dr. William J. Hitschler, and Dr. Chevalier L. Jackson.

PHILIPPINE SOCIETY OF OTOLARYNGOLOGY AND BRONCHO-ESOPHAGOLOGY.

President: Dr. Cesar F. Villafuerte.
Vice-President: Dr. Napoleon C. Ejercito.
Secretary-Treasurer: Dr. Eusebio E. Llamas.
Directors: Dr. Antonio L. Roxas and Dr. Armando T. Chiong.

PITTSBURGH OTOLOGICAL SOCIETY.

President: Dr. Emory A. Rittenhouse, 203 Masonic Bldg., McKeesport, Pa.
Vice-President: Dr. Carson S. Demling, 513 Jenkins Bldg., Pittsburgh 22, Pa.
Secretary-Treasurer: Dr. Clyde B. Lamp, 8101 Jenkins Arcade, Pittsburgh 22, Pa.

PORTUGUESE OTORHINOLARYNGOLOGICAL SOCIETY.

President: Dr. Albert Luis de Mendonca.
Secretary: Dr. Antonio da Costa Quinta, Avenida, de Liberdale 65, 1° Lisbon.

PUGET SOUND ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. Clifton E. Benson, Bremerton, Wash.
President-Elect: Dr. Carl D. F. Jensen, Seattle, Wash.
Secretary: Dr. Willard F. Goff, 1215 Fourth Ave., Seattle, Wash.

SIXTH INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST.

Meeting: University of Vienna, August 29 to September 1, 1960.

RESEARCH STUDY CLUB OF LOS ANGELES, INC.

Chairman: Dr. Orrie E. Ghrist, 210 N. Central Ave., Glendale, Calif.
Treasurer: Dr. Norman Jesberg, 500 So. Lucas Ave., Los Angeles 17, Calif.
Otolaryngology: Dr. Russell M. Decker, 65 N. Madison Ave., Pasadena 1, Calif.
Ophthalmology: Dr. Warren A. Wilson, 1930 Wilshire Blvd., Los Angeles 57, Calif.
Mid-Winter Clinical Convention annually, the last two weeks in January at Los Angeles, Calif.

SECTION ON OTOLARYNGOLOGY OF THE MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA.

Chairman: Dr. Morris E. Krucoff.
Vice-Chairman: Dr. Max J. Fischer.
Secretary: Dr. Adrian J. Delaney.
Treasurer: Dr. Robert D. Ralph.
Meetings are held the second Tuesday of September, November, January, March and May, at 6:30 P.M.
Place: Army and Navy Club, Washington, D. C.

SCOTTISH OTOLARYNGOLOGICAL SOCIETY.

President: Dr. F. T. Land, 13 Newton Place, Glasgow, C. 3.
Secretary-Treasurer: Dr. J. F. Birrell, 14 Moray Place, Edinburgh.
Assistant Secretary: Dr. H. D. Brown Kelly, 11 Sandyford Place, Glasgow, C. 3.

SOCIEDAD COLUMBIANA DE OFTALMOLOGIA Y OTORRINOLARINGOLOGIA (BOGOTA, COLUMBIA).

Presidente: Dr. Alfonso Tribin P.
Secretario: Dr. Felix E. Lozano.
Tesorero: Dr. Mario Arenas A.

SOCIEDAD CUBANA DE OTO-LARINGOLOGIA.

President: Dr. Reinaldo de Villiers.
Vice-President: Dr. Jorge de Cárdenas.
Secretary: Dr. Pablo Hernandez.

SOCIEDAD DE ESTUDIOS CLINICOS DE LA HABANA.

Presidente: Dr. Frank Canosa Lorenzo.
Vice-Presidente: Dr. Julio Sanguily.
Secretario: Dr. Juan Portuondo de Castro.
Tesorero: Dr. Luis Ortega Verdes.

SOCIEDAD DE OTORRINOLARINGOLOGIA Y BRONCOESOFAGOSCOPIA DE CORDOBA.

Presidente: Dr. Aldo Remorino.
Vice-Presidente: Dr. Luis E. Olsen.
Secretario: Dr. Eugenio Romero Diaz.
Tesorero: Dr. Juan Manuel Pradales.
Vocales: Dr. Osvaldo Suárez, Dr. Nondier Asis R., Dr. Jorge Bergallo Yofre.

SOCIEDAD DE OTO-RINO-LARINGOLOGIA, COLEGIO MEDIO DE EL SALVADOR, SAN SALVADOR, C. A.

President: Dr. Salvador Mixco Pinto.
Secretary: Dr. Daniel Alfredo Alfaro.
Treasurer: Dr. Antonio Pineda M.

SOCIEDAD ESPANOLA DE OTORRINOLARINGOLOGIA.

Presidente: Dr. D. Adolfo Hinojar Pons.
Vice-Presidente: Dr. D. Jose Perez Mateos.
Secretario General: Dr. D. Francisco Marañés.
Tesorero: Dr. D. Ernesto Alonso Ferrer.

SOCIEDAD MEXICANA DE OTORRINOLARINGOLOGIA
Monterrey 47-201
Mexico 7, D. F.

President: Dr. Rafael Giorgana.
Secretary: Dr. Carlos Valenzuela.
Treasurer: Dr. Benito Madariaga.
First Vocal: Dr. Rafael González.
Second Vocal: Dr. Juan Oberhauser.

SOCIEDAD NACIONAL DE CIRUGIA OF CUBA.

Presidente: Dr. Reinaldo de Villers.
Vice-Presidente: Dr. César Cabrera Calderin.
Secretario: Dr. José Xirau.
Tesorero: Dr. Alfredo M. Petit.
Vocal: Dr. José Gross.
Vocal: Dr. Pedro Hernández Gonzalo.

SOCIEDAD OTO-RINO-LARINGOLOGIA DE LOS HOSPITALES DE MADRID.

Presidente: Dr. Don Fernando Beltrán Castillo.
Secretario General: Dr. Don Alfonso Vassallo de Mumbert.
Tesorero: Dr. Don Rafael Garcia Tapia.

SOCIEDAD DE OTORRINOLARINGOLOGIA Y BRONCOESOFAGOLOGIA DEL NORESTE.

Presidente: Dr. Livio M. Lataza C.
Secretario: Dr. Ramón Prieto.
Tesorero: Dr. José Gomez Galizia.
Vocales: Dres. Enrique del Buono y O. Benjamin Serrano.

SOCIEDAD VENEZOLANA DE OTORRINOLARINGOLOGIA.

Presidente: Dr. Gabriel Briceño Romero.
Vice-Presidente: Dr. Silvestre Rincón Fuenmayor.
Secretario General: Dr. Oscar Bustamante Miranda.
Tesorero: Dr. Arturo Marrero Gómez.
Vocales: Dr. Miguel Octavio Russa, Dr. Benjamin Briceño, Dr. Oscar Gonzalez Castillo.

SOCIEDADE DE OFTALMOLOGIA E OTORRINOLARINGOLOGIA DO RIO GRANDE DO SUL.

President: Dr. Ivo Adolpho Kuhl.
Secretary: Dr. Decio Lisboa Castro.
Treasurer: Dr. Jorge Valentin.

SOCIEDAD PANAMENA DE OTORRINOLARINGOLOGIA.

Presidente: Dr. Manuel Preciado.
First Vice-Presidente: Dr. Alonso Roy.
Second Vice-Presidente: Dr. Carlos Arango Carbone.
Secretario: Dr. María Esther Villalaz.
Tesorero: Dr. Ramòn Crespo.

SOCIEDADE PORTUGUESA DE OTORRINOLARINGOLOGIA E DE BRONCO-ESOFAGOLOGIA.

Presidente: Dr. Alberto Luis De Mendonca.
Vice-Presidente: Dr. Jaime de Magalhaes.
1.° Secretario: Dr. Antonio da Costa Quinta.
2.° Secretario: Dr. Albano Coelho.
Tesoureiro: Dr. Jose Antonio de Campos Henriques.
Vogais: Dr. Teofilo Esquivel.
Dr. Antonio Cancela de Amorim.
Sede: Avenida da Liberdade, 65, 1°, Lisboa.

SOCIETY OF MILITARY OTOLARYNGOLOGISTS.

President: Lt. Col. Stanley H. Bear, USAF (MC), USAF Hospital, Maxwell (Air University), Maxwell Air Force Base, Ala.
Secretary-Treasurer: Capt. Maurice Schiff, MC, USN, U. S. Naval Hospital, Oakland, Calif.
Meeting:

SOUTH CAROLINA SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. L. D. Lide, Florence, S. C.
President-Elect: Dr. Harry Ross, Anderson, S. C.
Vice-President: Dr. David Stack, Spartanburg, S. C.
Secretary-Treasurer: Dr. Roderick Macdonald, Rock Hill, S. C.
Meeting: Jointly with the North Carolina Eye, Ear, Nose and Throat Society in Greenboro, N. C. Headquarters will be in the King Cotton Hotel, Sept. 13-15, 1960.

SOUTH WESTERN LARYNGOLOGICAL ASSOCIATION. (United Kingdom)

President: Mr. Michael Robert Sheridan, F.R.C.S., 7 Strangways Terrace, Truro, Cornwall.
Secretary and Treasurer: Mr. James Freeman, F.R.C.S., 22 Downs Park West, Bristol, 6.

SOUTHERN MEDICAL ASSOCIATION, SECTION ON OPHTHALMOLOGY AND OTOLARYNGOLOGY.

Chairman: Dr. George M. Haik, Professor and Head of the Department of Ophthalmology at Louisiana State University School of Medicine, 812 Maison Blanche Building, New Orleans 16, La.
Chairman-Elect: Dr. Mercer G. Lynch, Assistant Professor of Otolaryngology, Tulane University School of Medicine, 3503 Prytania St., New Orleans 15, La.
Vice-Chairman: Dr. Bernard J. McMahon, Director of the Department and Clinical Professor of Otolaryngology, St. Louis University School of Medicine, 8230 Forsythe Blvd., Clayton 24, Mo.

Secretary: Dr. Albert C. Esposito, First Huntington National Bank Building, Huntington, W. Va. Formerly instructor of Ophthalmology, Ohio State University College of Medicine, Columbus, O.
Meeting: St. Louis, Mo., October 31, 1960, to November 3, 1960.

VIRGINIA SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. Benjamin Sheppard, 301 Medical Arts Building, Richmond, Va.
President-Elect: Dr. Emanuel U. Wallerstein, Professional Building, Richmond, Va.
Vice-President: Dr. Calvin T. Burton, Medical Arts Building, Roanoke, Va.
Secretary-Treasurer: Dr. Maynard P. Smith, 600 Professional Building, Richmond, Va.

WEST VIRGINIA ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. Nime K. Joseph, Wheeling, W. Va.
President-Elect: Dr. John A. B. Holt, Charleston, W. Va.
Vice-President: Dr. William K. Marple, Huntington, W. Va.
Secretary-Treasurer: Dr. Albert C. Esposito, Huntington, W. Va.
Director for Two Years: Dr. James T. Spencer, Charleston, W. Va.